Clinical Equivalency of Ciprofloxacin 750 mg Enterally and 400 mg Intravenously for Patients Receiving Enteral Feeding: Systematic Review

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ABSTRACT

Background: Concomitant enteral administration of ciprofloxacin with products containing magnesium, aluminum, and calcium (e.g., as enteral feeds) decreases the oral bioavailability of this antibiotic. The manufacturer currently recommends holding enteral feeds for a total of 8 h after ciprofloxacin is given, but this is not feasible for patients who are receiving continuous enteral feeding. A previous study demonstrated that a higher dose of oral ciprofloxacin (750 mg BID) may compensate for the reduced bioavailability associated with this drug–food interaction, allowing adequate concentrations for effective bactericidal activity.

Objective: To evaluate whether ciprofloxacin 750 mg administered enterally is a clinically feasible alternative to ciprofloxacin 400 mg administered intravenously for adults receiving enteral feeds.

Methods: A literature search was conducted in EMBASE (January 1980 to April 2008) and MEDLINE (January 1949 to April 2008), with no language restrictions, using the key words "ciprofloxacin", "fluoroquinolone", "tube feed", and "enteral". For trials that remained after screening of the abstract, the full text was reviewed and the reference lists were hand-searched to identify additional trials. The following outcomes were prespecified: death, serious adverse events, clinical cure, microbiological cure, re-infection, total adverse events, ratio of area under the curve (AUC, in microgram-hours per millilitre) to minimum inhibitory concentration (MIC, in micrograms per millilitre), ratio of maximum serum concentration (C_{max}, in micrograms per millilitre) to MIC, and C_{max}.

Results: The search identified 121 potentially eligible studies, which were screened on the basis of information provided in the abstract. From this initial screening, it was clear that 113 studies did not meet the inclusion criteria. The remaining 8 studies were subjected to a full-text review, which revealed that only 1 study met the inclusion criteria. In that study, ciprofloxacin 750 mg given enterally yielded an AUC similar to that achieved with 400 mg given parentally, but the C_{max} was lower. No clinical outcomes were reported.

Conclusions: There is insufficient evidence from this systematic review to determine whether patients receiving enteral feeds concomitantly with

RÉSUMÉ

Contexte : L'administration concomitante par voie entérale de ciprofloxacine et de produits contenant du magnésium, de l'aluminium et du calcium (comme les préparations pour l'alimentation entérale) diminue la biodisponibilité de cet antibiotique administré par voie orale. Le fabricant de la ciprofloxacine recommande de ne pas donner de préparations pour alimentation entérale dans les huit heures suivant l'administration de ciprofloxacine, ce qui n'est pas possible chez les patients qui reçoivent une alimentation entérale continue. Une étude antérieure a démontré que l'administration d'une plus forte dose de ciprofloxacine par voie orale (750 mg BID) pourrait compenser la diminution de la biodisponibilité de l'antibiotique qui est associée à cette interaction médicament-nourriture, ce qui permettait ainsi l'atteinte de concentrations ayant un effet bactéricide efficace.

Objectif : Évaluer si l'administration d'une dose de 750 mg de ciprofloxacine par voie entérale constitue une solution de rechange cliniquement possible à une dose de 400 mg administrée par voie intraveineuse chez des adultes recevant une alimentation entérale.

Méthodes : Une recherche bibliographique a été effectuée dans les bases de données EMBASE (de janvier 1980 à avril 2008) et MEDLINE (de janvier 1949 à avril 2008), sans restriction linguistique, avec les mots clés « ciprofloxacine », « fluoroquinolone », « alimentation par sonde » et « entéral ». Pour les études cliniques toujours admissibles après avoir examiné leur résumé, le texte intégral des articles a été passé en revue et leur bibliographie a été scrutée pour repérer d'autres études pertinentes. Les résultats cliniques suivants ont été préétablis : mort, effets indésirables graves, guérison clinique, éradication microbiologique, réinfection, effets indésirables totaux, rapport de l'aire sous la courbe (ASC, en microgrammes-heures par millilitre) à la concentration inhibitrice minimale (CIM, en microgrammes per millilitre), rapport de la concentration sérique maximale (C_{max}, en microgrammes par millilitre) à la CIM, et C_{max}.

Résultats : La recherche a permis de trouver 121 études dont l'information fournie dans le résumé a été examinée pour en confirmer l'admissibilité. Cet examen préliminaire a permis de certifier que 113 de ces études ne répondaient pas aux critères d'inclusion. La revue du texte intégral des huit études restantes a révélé qu'une seule satisfaisait aux critères d'admissibilité. Dans cette étude, une dose de 750 mg de ciprofloxacine administrée par voie entérale a entraîné une ASC semblable à celle

enteral ciprofloxacin 750 mg BID will achieve clinical outcomes similar to those receiving parenteral ciprofloxacin 400 mg BID.

Key words: enteral feed, ciprofloxacin, quinolone, dosing regimen

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observée avec la dose de 400 mg administrée par voie parentérale, mais la C_{max} était cependant plus faible. Aucun résultat clinique n'a été mentionné dans cette étude.

Conclusions : Les données de cet examen systématique ne sont pas suffisantes pour déterminer si les patients qui sont alimentés par voie entérale et qui reçoivent en concomitance une dose de ciprofloxacine de 750 mg BID par voie entérale obtiendront des résultats cliniques semblables à ceux qu'ils obtiendraient avec une dose de 400 mg BID par voie parentérale.

Mots clés : alimentation entérale, ciprofloxacine, quinolone, régime posologique

[Traduction par l'éditeur]

INTRODUCTION

Economic studies have shown that oral administration of antibiotics reduces drug costs.[1] The advantages of oral or enteral antibiotic administration include ease of administration, ability to continue therapy in an outpatient setting, and reduced IV-related complications, such as excess fluid administration, local or systemic infection, phlebitis, and patient discomfort.[2]

It is well known that concomitant oral or enteral administration of ciprofloxacin with products containing magnesium, aluminum, and calcium (e.g., nutritional supplements or enteral feeds) decreases the oral bioavailability of the ciprofloxacin. It is postulated that divalent ions bind to the ciprofloxacin, forming an insoluble complex in the gastrointestinal tract.[3,4] This drug–food interaction reduces the efficacy of ciprofloxacin and may lead to treatment failure, posing a risk for breakthrough septicemia or emergence of drug resistance.[5] Therefore, the manufacturer's current recommendation is to administer ciprofloxacin 2 h before and 6 h after enteral feeding.[3] However, this is clinically impractical, since the usual dosing frequency for the drug is twice daily; holding enteral feeds for a total of 16 h/day would not allow sufficient nutritional intake for patients receiving enteral feeding. Common clinical practice is to hold feeds for 2 h before and 2 h after administration of ciprofloxacin, despite the potential risk of treatment failure through reduction of serum ciprofloxacin concentration. Therefore, alternative approaches must be sought to reduce the complications associated with holding feeds.

Published studies of hospital inpatients allow assessment of the effects of enteral feeding on the oral bioavailability of ciprofloxacin. Anecdotal information suggests that a higher dose of oral ciprofloxacin (750 mg BID) might compensate for reduced bioavailability and yield adequate plasma concentration for effective bactericidal activity. In a study comparing doses of 500 mg and 750 mg BID given enterally, Debon and others[6] determined that both doses achieved sufficient area under the curve (AUC) and maximum serum concentration (C_{max}) for commonly encountered organisms (e.g., *Escherichia coli*). However, for less susceptible pathogens, such as *Pseudomonas* spp. and *Staphylococcus aureus*, the authors stated that the higher dose of ciprofloxacin should be used. To date, no systematic review has been published to evaluate the relative efficacy and safety of ciprofloxacin 750 mg given enterally and ciprofloxacin 400 mg given intravenously for patients who are receiving continuous enteral feeding. Anecdotal information from local clinicians indicated that the 750-mg dose is being used and that, contrary to the manufacturer's recommendations, enteral feeds are not being held.

The aim of this systematic review was to gather and summarize existing evidence to evaluate the efficacy of ciprofloxacin 750 mg administered enterally and 400 mg administered intravenously in patients receiving enteral feeds.

METHODS

Research Question

Is ciprofloxacin 750 mg administered enterally a clinically feasible alternative to ciprofloxacin 400 mg administered intravenously for adults receiving enteral feeds?

Hierarchy of Clinical Outcomes

In descending order of importance, the clinical outcomes of interest were death, serious adverse events, clinical cure, microbiological cure, re-infection, total adverse events, ratio of AUC to minimum inhibitory concentration (MIC), ratio of C_{max} to MIC, and C_{max}.

Data Extraction

The review was undertaken by all 3 authors (D.C., L.C., A.T.). Two of the authors (L.C., A.T.) independently searched the literature and screened the articles to identify studies that satisfied the inclusion criteria. The same 2 authors extracted the data using a standardized data extraction form; the third author (D.C.) was consulted to resolve discrepancies.

Inclusion Criteria

To be included in this review, studies had to be full reports of published, randomized controlled trials in which patients were randomly assigned to receive either ciprofloxacin 750 mg enterally or ciprofloxacin 400 mg intravenously in the presence of enteral feeding (i.e., feeds administered through a nasojejunal, nasoduodenal, nasogastric, or an orogastric tube). For the specified study question, a randomized controlled trial with parallel groups comparing 750 mg given enterally with 400 mg given intravenously, with reporting of clinical outcomes, was considered ideal. If no trials with clinical outcomes were found, randomized cross-over trials were included, because participants in a cross-over trial serve as their own controls. As such, confounding of results due to interindividual variability in pharmacokinetic parameters would be minimized. In addition, included trials must have reported on at least one of the prespecified outcomes (as stated above).

Participants

Patients had to be adults admitted to hospital with any acute infection requiring ciprofloxacin therapy. Trials involving healthy volunteers were excluded, as the primary focus of this systematic review was the effect of different doses on clinical outcomes. In addition, the pharmacodynamic and pharmacokinetic effects of drugs differ between patients with acute illness and healthy volunteers.

Searches

Searches were conducted in EMBASE (January 1, 1980, to April 28, 2008) and MEDLINE (January 1, 1949, to April 28, 2008). No language restrictions were applied. The following key words were used: "ciprofloxacin", "fluoroquinolone", "tube feed", and "enteral". In addition, the reference lists of trials that underwent full-text review were hand-searched to identify additional trials.

RESULTS

The search identified 121 potentially eligible studies that focused on ciprofloxacin. Initial screening of the abstracts clearly indicated that 113 of these trials did not meet the inclusion criteria. The remaining 8 studies were subjected to a full-text review because the abstracts did not provide sufficient information to assess whether they met the inclusion criteria. One additional trial, by Yuk and others,[7] was identified by hand-searching the reference list in the report by Mimoz and others.[5] After review, 7 of the 8 studies were excluded. Details about the included trial[8] appear in Table 1 and those for the 7 excluded trials[1,5,6,7,9-11] are given in Table 2. The detailed results of the excluded studies are presented in Appendix 1 to give the reader a complete picture of the available evidence. All 8 studies assessed pharmacokinetic parameters, but none assessed clinical outcomes (Table 1, Table 2). Among the 7 excluded studies, 5 trials concluded that 750 mg BID given enterally may be used, whereas 2 trials concluded that this dosage regimen may result in a serum concentration that would be insufficient for bactericidal activity.

Because the search strategy included the key word "fluoroquinolone", 2 articles about other quinolones were identified and retrieved. In the study by Burkhardt and others,[12] healthy volunteers were randomly assigned to receive either moxifloxacin 400-mg tablet orally with water, moxifloxacin 400-mg tablet with water through a nasogastric tube, or moxifloxacin 400-mg tablet with enteral feeds through a nasogastric tube. Kanji and others[13] randomly assigned patients who were undergoing tube feeding to receive gatifloxacin either 400 mg IV or 400 mg through a nasogastric tube. Neither of these trials met the inclusion criteria, and they were excluded from analysis in the systematic review. Nonetheless, these trials are summarized in Table 2, and the study by Kanji and others[13] is considered in the Discussion, as it provides insight into the topic.

Included Study

The study by De Marie and others[8] was the only randomized cross-over pharmacokinetic study comparing ciprofloxacin 400

Table 1. Summary of Included Study

			Mean AUC (95% CI) (μg · h/mL)		Mean C_{max} (95% CI) (μg/mL)		Mean T_{max} (95% CI) (h)	
Reference	**Intervention**	**Comparator**	**Intervention**	**Comparator**	**Intervention**	**Comparator**	**Intervention**	**Comparator**
De Marie et al.[8]	Ciprofloxacin 400 mg IV BID	Ciprofloxacin 750 mg BID enterally	19.3 (11.8–26.7)	19.1 (10.8–27.5)	6.8 (3.9–9.8)	3.2 (1.8–4.6)	2.1 (0.4–3.8)	0.6 (0.3–0.9)

AUC = area under the curve, CI = confidence interval, C_{max} = maximum serum concentration, T_{max} = time to maximum serum concentration.

Table 2. Summary of Excluded Studies

Reference	Reason for Exclusion	Type of Study	Population	*n*	Intervention	Comparator	Feeds and Rate	Authors' Conclusions
Ciprofloxacin studies								
Mimoz et al.[5]	Nonrandomized, cross-over, prospective trial	Prospective pharmaco-kinetic study of ciprofloxacin	Surgical ICU patients receiving continuous enteral feeds	12	Ciprofloxacin 400 mg IV BID, then stepped down to NG administration	Ciprofloxacin 750 mg BID by NG tube	Normo-Real fibres, Sodietal, Ploudaliel, France, at 60–80 mL/h	"Enteral ciprofloxacin could be given to patients requiring continuous enteral feeds provided that the NG dose is twice the parenteral one."
Debon et al.[6]	Did not compare with ciprofloxacin 400 mg given intravenously	Pharmaco-kinetic study comparing 2 ciprofloxacin doses using oral suspension; prospective; randomized	ICU patients with severe bacterial pneumonia	20	Ciprofloxacin 500 mg BID by NG tube	Ciprofloxacin 750 mg BID by NG tube	Fresenius Kabi, Sevres, France, at 60–80 mL/min	"For most pathogens, ciprofloxacin oral suspension at a dosage of 500 mg or 750 mg every 12 h reached satisfying pharmacokinetic parameters in tube-fed critically ill patients with bacterial pneumonia."
Healy et al.[9]	Did not compare with ciprofloxacin 400 mg given intravenously	Pharmaco-kinetic study of ciprofloxacin absorption; randomized, 2-period, 2-treatment, 2-sequence cross-over design in 3 patient groups	Inpatients given enteral feeds orally vs. G-tube vs. J-tube	26	Ciprofloxacin 500 mg in G-tube and J-tube; excluded oral group with intermittent feeds	Ciprofloxacin 500 mg with continuous feeds	Jevity ready-to-use, at 60–90 mL/h	"By administering via the g-tube route, the interaction with ciprofloxacin may not be clinically important as demonstrated by C_{max}; however, AUC is significantly reduced."
Yuk et al.[7]	Did not compare with ciprofloxacin 400 mg given intravenously	Pharmaco-kinetic study of ciprofloxacin comparing NG and nasoduodenal administration	ICU patients (except one), with normal renal and liver function and receiving enteral feeds	7	Ciprofloxacin 750 mg crushed in 40 mL of water, given q12h by nasoduodenal route	Ciprofloxacin 750 mg given by NG tube	Not specified	"Greater absorption when ciprofloxacin was administered directly into the duodenum as compared with its administration into the stomach."
Cohn et al.[10]	No comparator	Prospective pharmacokinetic study of bioavailability of ciprofloxacin during enteral feeding	ICU patients receiving ventilation and requiring antibiotics for pneumonia and who tolerated tube feeding for 48 h	7	Ciprofloxacin 750 mg BID for 48 h	None	Pulmocare; rate of infusion not specified	"The oral absorption of the 750 mg ciprofloxacin dose in critically ill patients was moderate, but variable, despite this, these serum levels were well above MICs for many important pathogenic bacteria."

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Table 2. Summary of Excluded Studies (continued)

Reference	Reason for Exclusion	Type of Study	Population	*n*	Intervention	Comparator	Feeds and Rate	Authors' Conclusions
Mueller et al.[1]	Comparator was ofloxacin; participants were healthy volunteers	Pharmaco-kinetic study of ciprofloxacin and ofloxacin with enteral Ensure feeds in healthy volunteers; randomized cross-over study (each patient received 4 treatments)	Healthy volunteers	13	Ciprofloxacin 750 mg and water 120 mL PO Ciprofloxacin 750 mg and enteral feed 120 mL PO q30 min for 5 doses	Ofloxacin 400 mg and water 120 mL PO Ofloxacin 400 mg and enteral feed 120 mL PO q30 min for 5 doses	Consumed 120 mL of Ensure, repeated every 30 min for a total of 5 doses	"Given the results of the present study, it appears that switching from parenteral antibiotics to oral ciprofloxacin in a patient who receives Ensure® could result in undesirably low concentrations in serum."
Yuk et al.[11]	Participants were healthy volunteers	Pharmaco-kinetic study bioavailability of ciprofloxacin administered via NG tube with and without enteral feeds in 6 healthy volunteers; randomized 3-way cross-over study	Healthy volunteers	6	Intact ciprofloxacin 750 mg PO	Crushed ciprofloxacin 750 mg suspension via NG tube; crushed ciprofloxacin 750 mg suspension via NG with enteral feeds	Osmolit delivered at 100 mL/h for 2 h before administration of drug	"Concurrent enteral feeding does not interfere with the absorption of ciprofloxacin and, thus, does not have to be interrupted when administering ciprofloxacin."
Studies of other fluoroquinosones								
Burkhardt et al.[12]	No ciprofloxacin arms; healthy volunteers given oral moxifloxacin with or without feeds (no comparison with intravenous moxifloxacin)	Pharmaco-kinetic study of bioavailability of moxifloxacin given with feeds, water, or alone. Open-label, randomized, controlled, 3-way cross-over study	Healthy volunteers	12	Intact moxifloxacin tablet 400 mg given orally	Crushed moxifloxacin tablet 400 mg given with water via NG tube and crushed moxifloxacin tablet given with enteral feeds via NG tube	Isosource Energy at 100 mL/h, 30 min before administration of drug	No clinically relevant effect of enteral feeding on pharmacokinetic parameters of moxifloxacin in healthy volunteers.
Kanji et al.[13]	No ciprofloxacin arms	Randomized single-dose cross-over study of gatifloxacin in critically ill patients receiving enteral feeds	Critically ill patients	16	Gatifloxacin 400-mg tablet, crushed, given with enteral feeds	Gatifloxacin 400 mg IV given to patients receiving enetral feeds	Jevity, Impact, Pulmocare, Promote, Impact brands, given at variable rates	Gatifloxacin given to critically ill patients via NG tube does not consistently yield high bioavailability.

AUC = area under the curve, C_{max} = maximum serum concentration, G-tube = gastric feeding tube, ICU = intensive care unit, J-tube = jejunostomy tube, MIC = minimum inhibitory concentration, NG = nasogastric.

mg IV BID with ciprofloxacin 750 mg BID given enterally (through nasogastric or nasoduodenal tube) and meeting all of the inclusion criteria. The authors reported the AUC, C_{max}, and time to maximum serum concentration (T_{max}) after steady state was achieved in 5 tube-fed patients with severe gram-negative intra-abdominal infections who were being treated in the intensive care unit (ICU). The study had a 36-h delay between measurements for each dosing regimen (which was appropriate, given the half-life of ciprofloxacin). Patients received either Nutrison, Nutrison E+, or Nutricia feeds at a rate of 50–75 mL/h. Detailed results of this trial are provided in Table 1. The authors concluded that "enteral administration of ciprofloxacin 750 mg BID during tube feeding in ICU patients with severe gram negative intra-abdominal infections resulted in serum levels comparable to those after 400 mg BID IV". However, this regimen may be insufficient for *Pseudomonas* infections, because that organism has a higher MIC.[8]

DISCUSSION

Ciprofloxacin can be administered enterally. Enteral administration is a desired alternative route for step-down therapy in patients who cannot eat but whose gastrointestinal tract is functioning. We identified 8 potentially eligible trials reporting on administration of different doses of ciprofloxacin to patients receiving continuous enteral feeds. On detailed examination, only one trial met the inclusion criteria. The other 7 trials were excluded because of various methodologic issues, such as lack of randomization, lack of a control group and/or lack of a cross-over design, study population of healthy volunteers, or lack of direct comparison of the treatment regimens outlined in the research question.

In the trials that have been performed to date, clinical outcomes have not been measured. Therefore, pharmacokinetic data must be extrapolated to evaluate the optimal dose of ciprofloxacin for patients receiving continuous enteral feeds. As such, an analysis of randomized cross-over trials is most appropriate. The only trial meeting this criterion that we identified was that of De Marie and others.[8] These authors reported the AUC, C_{max}, and T_{max} after steady state was achieved in 5 tube-fed patients with severe gram-negative intra-abdominal infections who were receiving ciprofloxacin either 400 mg BID intravenously or 750 mg BID enterally. All of the patients had either nasogastric or nasoduodenal tubes for enteral administration. Unfortunately, the authors did not differentiate the pharmacokinetic parameters according to whether the patients had nasogastric or nasoduodenal tubes. Absorption of ciprofloxacin may be more favourable in the duodenum, which may affect the AUC.[7] However, it has also been reported that ciprofloxacin is absorbed well in the upper gastrointestinal tract, with greater absorption in the stomach and duodenum than in the jejunum; as such, as long as the enteral tube is not placed beyond the jejunum, placement may not be clinically important.[14] De Marie and others[8] demonstrated that IV and enteral administration achieve similar AUC values, but the C_{max} for enterally administered ciprofloxacin is lower than that for the parenteral route. Unfortunately, these authors did not report patient-specific MIC values for the indicated organisms; therefore, we were unable to determine the patient-specific AUC/MIC and C_{max}/MIC ratios, which have been shown to correlate with clinical outcomes.[15] We could not extrapolate population MIC values to generate the AUC/MIC and C_{max}/MIC ratios, since population estimates of organism-specific MICs do not necessarily predict the outcome for individual patients in response to a particular antibiotic. The actual MIC values of the infective organism in a particular patient may be higher or lower than the estimated population MIC values.[16] Other limitations of the study by De Marie and others[8] were the small sample size (5 patients) and the fact that all patients had a gram-negative intra-abdominal infection, which limits the applicability of these results to other patient populations, including patients with other infections. Of note is the study by Kanji and others,[13] who analyzed the pharmacokinetic parameters of gatifloxacin in critically ill patients. This trial had a design similar to that of the study by De Marie and others.[8] Kanji and others[13] found that C_{max} levels for gatifloxacin were lower when tablets were given orally with enteral feeds than when the gatifloxacin was given intravenously; however, AUC levels were similar for the 2 dosage forms. Kanji and others[13] did not report patient-specific MICs for the indicated organisms; we were therefore unable to determine the patient-specific AUC/MIC and C_{max}/MIC ratios, nor could we make any suggestions about correlations with clinical outcomes according to different dosage forms.

Fluoroquinolones display unique pharmacodynamic properties, whereby the drugs exhibit both concentration-dependent and time-dependent bacterial killing. In previous studies, both C_{max}/MIC and AUC/MIC ratios reflected the effectiveness of quinolones, whereas the AUC/MIC ratio provided a better representation of the effectiveness of these drugs.[17] Providing maximal drug exposure allows eradication of bacteria and reduces the risk of antibiotic resistance.[18] Thus, the therapeutic goal is to maximize drug exposure, as represented by the extent of bioavailability from the AUC. Other studies have shown that a C_{max}/MIC ratio of at least 10 would eradicate bacteria,[17] and AUC/MIC ratios greater than 125 were associated with successful clinical outcomes.[19] In a retrospective study of IV ciprofloxacin treatment of seriously ill patients, Forrest and others[15] associated the AUC/MIC ratio with clinical and microbiological outcomes. They found that with an AUC/MIC ratio above 125, the probability of clinical cure was 80% and the probability of microbiological cure was 82%. However, debate continues as to whether AUC/MIC ratios are organism-specific. Some claim that gram-positive bacteria require an AUC/MIC ratio of 30–50 and gram-negative bacteria an AUC/MIC ratio of 100–125.[20] Others have stated that "at this time, it is clear that for different organisms, different free drug AUC/MIC ratios are desirable. Attempts to standardize exposure to one AUC/MIC ratio are erroneous."[21]

According to the guidelines of the Clinical and Laboratory Standards Institute (CLSI), *E. coli* and *Pseudomonas* are to be deemed susceptible if the MIC is less than or equal to 1 μg/mL. Susceptibility is defined as follows: "the isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the recommended dosage is used for the site of infection."[22] According to Mandell and others,[21] ciprofloxacin 500 mg administered orally achieves a C_{max} of 2.4 μg/mL, which is approximately twice the MIC breakpoint provided by the CLSI. De Marie and others[8] found a C_{max} of 3.2 μg/mL with ciprofloxacin 750 mg BID administered enterally, which would imply that this dose and route would

achieve adequate bactericidal activity against *E. coli* and *Pseudomonas*.[21] However, fluoroquinolones exhibit concentration-dependent killing; therefore, the higher the concentration, the greater the rate and extent of bactericidal activity.[20] With parenteral administration, these drugs achieve a C_{max} of 6.8 µg/mL and may exhibit greater bactericidal activity. Since data for organism-specific MIC were not reported by De Marie and others,[8] we do not know if a C_{max} of 3.2 or 6.8 µg/mL would achieve a C_{max}/MIC ratio of 10 or more for a particular organism that could be correlated with clinical outcomes.[18,20] Despite this limitation, parenteral and enteral administration achieved similar AUC values. Again, without organism-specific MICs, the AUC/MIC ratio (another predictor of clinical outcomes[17]) cannot be calculated for the patients in that trial. Therefore, it is unknown whether patients receiving ciprofloxacin 750 mg BID enterally or ciprofloxacin 400 mg BID intravenously will have similar clinical outcomes.

Implications for Practice

Because of the paucity of evidence for clinical equivalence, the choice to use ciprofloxacin 750 mg BID enterally should be based on a number of factors. Clinicians must consider the patient's clinical status, including the acuity of the patient's illness, signs and symptoms of clinical improvement or deterioration, and the site of infection. In particular, higher concentrations of the drug may be required for infections other than bacteremias and urinary tract infections.

Implications for Future Studies

The ideal trial would have the following characteristics: random assignment of patients receiving enteral feeds to either ciprofloxacin 400 mg BID intravenously, ciprofloxacin 500 mg BID enterally, or 750 mg BID enterally; and measurement of pertinent clinical outcomes, relevant microbiological data, and pharmacokinetic and pharmacodynamic parameters.

CONCLUSIONS

There is insufficient evidence to determine whether patients receiving enteral feeds who are given ciprofloxacin 750 mg BID enterally will achieve clinical outcomes similar to those of patients who receive ciprofloxacin 400 mg BID intravenously. There is evidence to suggest that when patients receiving continuous enteral feeds are given ciprofloxacin 750 mg BID enterally, they will achieve similar AUCs but lower C_{max} concentrations relative to patients who receive ciprofloxacin 400 mg BID intravenously.

References

1. Mueller BA, Brierton DG, Abel SR, Bowman L. Effect of enteral feeding with Ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. *Antimicrob Agents Chemother* 1994;38(9):2101-2105.
2. MacGregor RR, Graziani AL. Oral administration of antibiotics: a rational alternative to the parenteral route. *Clin Infect Dis* 1997; 24(3):457-467.
3. *Compendium of pharmaceuticals and specialties* [online version]. Ottawa (ON): Canadian Pharmacists Association; 2008.
4. Ciprofloxacin. In: *AHFS drug information 2008*. Bethesda (MD): American Society of Health-System Pharmacists; 2008.
5. Mimoz O, Binter V, Jacolot A, Edouard A, Tod M, Petitjean O, et al. Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with continuous enteral feeding to critically ill patients. *Intensive Care Med* 1998;24(10):1047-1051.
6. Debon R, Brielh D, Boselli H, Saux MC, Duflo F, Chassard D, et al. Pharmacokinetic parameters of ciprofloxacin (500 mg/5 mL) oral suspension in critically ill patients with severe bacterial pneumonia: a comparison of two dosages. *J Chemother* 2002;14(2):175-180.
7. Yuk JH, Nightingale CH, Quintiliani R, Yeston NS, Orlando R 3rd, Dobkin ED, et al. Absorption of ciprofloxacin administered through a nasogastric or a nasoduodenal tube in volunteers and patients receiving enteral nutrition. *Diagn Microbiol Infect Dis* 1990;13(2):99-102.
8. de Marie S, VandenBergh MF, Buijk SL, Bruining HA, van Vliet A, Kluytmans JA, et al. Bioavailability of ciprofloxacin after multiple enteral and intravenous doses in ICU patients with severe gram-negative intra-abdominal infections. *Intensive Care Med* 1998;24(4):343-346.
9. Healy DP, Brodbeck MC, Clendening CE. Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother* 1996;40(1):6-10.
10. Cohn SM, Sawyer MD, Burns GA, Tolomeo C, Milner KA. Enteric absorption of ciprofloxacin during tube feeding in the critically ill. *J Antimicrob Chemother* 1996;38(5):871-876.
11. Yuk JH, Nightingale CH, Sweeney KR, Quintiliani R, Lettieri JT, Frost RW. Relative bioavailability in healthy volunteers of ciprofloxacin administered through a nasogastric tube with and without enteral feeding. *Antimicrob Agents Chemother* 1989;33(7):1118-1120.
12. Burkhardt O, Stass H, Thuss U, Borner K, Welte T. Effects of enteral feeding on the oral bioavilability of moxifloxacin in healthy volunteers. *Clin Pharmacokinet* 2005;44(9):969-976.
13. Kanji S, McKinnon PS, Barletta JF, Kruse JA, Devlin JW. Bioavailability of gatifloxacin by gastric tube administration with and without concomitant enteral feeding in critically ill patients. *Crit Care Med* 2003;31(5):1347-1352.
14. Harder S, Fuhr U, Beermann D, Staib AH. Ciprofloxacin absorption in different regions of the human gastrointestinal tract. Investigations with the hf-capsule. *Br J Clin Pharm* 1990;30(1):35-39.
15. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993;37(5):1073-1081.
16. Schentag JJ, Meagher AK, Forrest A. Fluoroquinolone AUIC break points and the link to bacterial killing rates. Part 2: human trials. *Ann Pharmacother* 2003;37(10):1478-1488.
17. Roberts JA, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin Pharmacokinet* 2006;45(8):755-773.
18. Nicolau DP. Optimizing outcomes with antimicrobial therapy through pharmacodynamic profiling. *J Infect Chemother* 2003;9(4):292-296.
19. Frei CR, Wiederhold NP, Burgess DS. Antimicrobial breakpoints for gram-negative aerobic bacteria based on pharmacokinetic–pharmacodynamic models with Monte Carlo simulation. *J Antimicrob Chemother* 2008;61(3):621-628.
20. Lewis DA, Davis GA, Ensom MHH, editors. *Clinical pharmacokinetics service and anticoagulation guidelines: Pharmacy Services University of Kentucky HealthCare.* 29th ed. Lexington (KY): University of Kentucky Chandler Medical Center, Department of Pharmacy Services; 2007 Jul.
21. Mandell GL, Bennett JE, Dolin R. *Principles and practice of infectious diseases.* 6th ed. Philadelphia (PA): Churchill Livingston; 2005.
22. *Performance standards for antimicrobial susceptibility testing*; *18th informational supplement*. 18th ed. Wayne (PA): Clinical and Laboratory Standards Institute; 2008.

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Appendix 1. Summary of Results From Excluded Studies*

	Mean AUC ± SD† (μg · h/mL)		Mean C_{max} ± SD† (μg/mL)		Mean C_{min} ± SD† (μg/mL)		Mean T_{max} ± SD† (h)	
Reference	**I**	**C**	**I**	**C**	**I**	**C**	**I**	**C**
Mimoz et al.[5]‡	Median 10.3 (IQR 3.3–34.6) Mean 13.6§	Median 8.4 (IQR 3.6–53.4) Mean 12.8§	Median 4.1 (IQR 1.5–7.4) Mean 4.4§	Median 2.3 (IQR 0.7–5.8) Mean 3.4§	Median 0.2 (IQR 0.1–1.4) Mean 0.3§	Median 0.2 (IQR 0.1–2.4) Mean 0.4§	Median 0.9 (IQR 0.75–1.00) Mean 0.85§	Median 1.25 (IQR 0.75–3.33) Mean 1.48§
Debon et al.[6]	24.7 (95% CI 12.9–36.2)	28.9 (95% CI 18.3–47.5)	2.6 (95% CI 1.2–4.3)	3.51 (95% CI 1.5–5.9)	0.4 (95% CI 0.1–0.9)	0.6 (95% CI 0.4–1.0)	1.8 (95% CI 1.5–3.0)	1.9 (95% CI 1.0–3.0)
Healy et al.[9]	G-tube: 15.9±6.62 J-tube: 18.1±9.37	G-tube: 7.44±3.16 J-tube: 5.82±2.63	G-tube: 3.68±1.36 J-tube: 3.78±1.87	G-tube: 2.27±0.67 J-tube: 1.45±0.48	NA	NA	G-tube: 1.0 (0.5–1.5) J-tube 0.5 (0.5–1.5) Reported median‡	G-tube 0.5 (0.5–1.5) J-tube 1.0 (0.5–1.0)
Yuk et al.[7]	25.35±8.35	11.27±5.39	4.6±1.11	2.57±1.00	NA	NA	Achieved rapidly in both groups	
Cohn et al.[10]	10.63±2.11	NA	2.23±0.39	NA	NA	NA	1.04±0.22	NA
Mueller et al.[1]	Cipro + Ensure 11.66±3.7 (7.24–17.29) Cipro + water 15.96±3.12 (11.5–23.27)	Ofloxacin + Ensure 36.37±9.98 (23.43–65.13) Ofloxacin + water 40.42±11.01 (27.39–73.54)	Cipro + Ensure: 1.99±0.57 (1.37–3.34) Cipro + water: 3.79±0.72 (2.18–5.07)	Ofloxacin + Ensure: 3.48±0.84 (2.16–5.10) Ofloxacin + water: 5.47±1.18 (3.13–7.39)	NA	NA	Cipro + Ensure: 2.42±1.12 (1–4) Cipro + water: 0.92±0.19 (0.5–1)	Ofloxacin + Ensure: 2.04±1.47 (0.5–6) Ofloxacin + water: 0.81±0.69 (0.5–3)
Yuk et al.[11]	Cipro PO 13.17±4.81	Cipro NG 11.46±4.51 Cipro NG and enteral feeds 15.02±3.79	Cipro PO 2.80±0.94	Cipro NG 2.12±0.37 Cipro NG and enteral feeds 2.92±0.78	NA	NA	Cipro PO 0.75±0.27	Cipro NG 1.33±0.52 Cipro NG and enteral feeds 1.25±0.94
Burkhardt et al.[12]	Moxi PO 39.6±1.13	Moxi with feeds, NG 36.1±1.12	Moxi PO 3.20±1.12	Moxi with feeds, NG 2.83±1.15	NA	NA	Moxi PO median 1.75 (IQR 0.50–4.00)	Moxi with feeds NG median 1.75 (IQR 0.50–3.00)
Kanji et al.[13] (mean and 95% CI)	Gati NG ITF 38.0 (20.1–48.5) CTF 34.2 (23.9–85.5)	Gati IV ITF 39.5 (24.1–63.1) CTF 39.7 (22.5–63.1) mean and 95% CI	Gati NG ITF 2.62 (1.15–6.60) CTF 3.31 (2.18–6.60)	Gati IV ITF 4.65 (3.03–7.78) CTF 4.45 (3.05–5.39)	NA	NA	Gati NG ITF 1.03 (0.53–7.79) CTF 1.50 (0.47–2.67)	Gati IV NA

AUC = area under the curve, C = comparator, CI = confidence interval, Cipro = ciprofloxacin, C_{max} = maximum serum concentration, C_{min} = minimum serum concentration, CTF = continuous tube feeding, Gati = gatifloxacin, G-tube = gastric feeding tube, J-tube = jejunostomy tube, I = intervention, IQR = interquartile range, ITF = intermittent tube feeding, Moxi = moxifloxacin, NA = not applicable, NG = nasogastric, SD = standard deviation, T_{max} = time to maximum serum concentration.
*For all studies, percent clinical and microbiological cure were not applicable. Recurrence and resistance were also not applicable.
†Except where indicated otherwise.
‡Some information was not reported in the published article, but was obtained from the original authors.
§Calculated by authors of current study.