11-1996

Enteric Absorption of Ciprofloxacin During Tube Feeding in the Critically Ill

Stephen M. Cohn

Mark D. Sawyer

Gerard A. Burns

Concertina Tolomeo

Kerry A. Milner
Sacred Heart University, milnerk@sacredheart.edu

Recommended Citation

Cohn, Stephen M. et. al. "Enteric Absorption of Ciprofloxacin During Tube Feeding in the Critically Ill." Journal of Antimicrobial Chemotherapy 38.5 (1996): 871-876.

Journal of Antimicrobial Chemotherapy (1996) **38**, 871–876

Enteric absorption of ciprofloxacin during tube feeding in the critically ill

Stephen M. Cohn*, Mark D. Sawyer, Gerard A. Burns, Concettina Tolomeo and Kerry A. Milner

Section of Trauma/Surgical Critical Care, Department of Surgery, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA

To determine the pharmacokinetic properties of ciprofloxacin in the critically ill, we studied seven mechanically ventilated patients with pneumonia during enteral feedings. Subjects received ciprofloxacin 750 mg every 12 h via nasogastric tube and serial serum drug concentrations were measured after the first and fourth dose. After the initial dose, the maximum serum concentration ranged from 1.24–3.06 mg/L, and the area under the time curve from 0–12 h ranged from 3.2–19.65 mg.h/L. Similar levels were noted after dose four. Gastrointestinal absorption of ciprofloxacin in tube fed critically ill patients was decreased, but well above MIC values for many pathogenic bacteria.

Introduction

Ciprofloxacin has been demonstrated to have broad antimicrobial activity, excellent tissue penetration, long duration of action and good bioavailability (Bergan, 1988). These factors increase the likelihood of therapeutic efficacy and make oral ciprofloxacin a potential alternative to parenteral antibiotics in patients with functioning gastrointestinal tracts. Ciprofloxacin may be particularly useful in treatment of nosocomial respiratory tract infections because most respiratory tract pathogens are susceptible. A large multicentre trial showed parenteral ciprofloxacin to be as efficacious (69% clinical response rate) as imipenem-cilastatin (59%) in the treatment of severe nosocomial pneumonia (Fink *et al.*, 1994). Studies have also shown the oral form of ciprofloxacin to have comparable cure rates to parenteral antibiotics in the sequential treatment (parenteral followed by oral form) of serious bacterial respiratory tract infections, limiting the need for parenteral antibiotics and leading to substantial cost savings (Khan & Basir, 1989; Paladino *et al.*, 1991).

Previously, we demonstrated that gastrointestinal absorption of ciprofloxacin is unpredictable in critically ill patients immediately after major abdominal procedures, when gut function is diminished (Cohn *et al.*, 1995). We felt that critically ill patients

*Tel: +1(203)-785-2572; Fax: +1(203)-785-3950.

0305–7453/96/110871 + 06 $12.00/0

with functioning gastrointestinal tracts, as demonstrated by tolerance of tube feedings, would be likely to absorb oral drugs. Therefore, we hypothesized that ciprofloxacin administered via nasogastric tube would be sufficiently absorbed to achieve therapeutic serum concentrations in this intensive care unit population.

Materials and methods

Antibacterial agent

Ciprofloxacin (Bayer Corp., Pharmaceutical Division, West Haven, CT, USA) was administered in 750 mg doses via nasogastric tube every 12 h for 48 h (total of four doses). The tablets were pulverized and added to 50 mL of sterile water before administration. The nasogastric tube was flushed with 30 mL of sterile water to ensure that the entire dose was delivered into the stomach. After introduction of the drug into the stomach, the nasogastric tube was reattached to the feeding pump and Pulmocare enteral feedings were resumed. No other oral medications (e.g., carafate or antacids) were given during this study. The patients received stress ulcer prophylaxis in the form of H_2 receptor antagonists, intravenously.

Subjects

Seven subjects (two female, five male) with a mean age of 52 years (range 34–71) consented to participate in this investigation. Subjects were included in the study if they were at least eighteen years of age, required mechanical ventilation, were receiving parenteral antibiotics for treatment of a documented pneumonia (fever, leukocytosis, positive sputum, and new infiltrate on chest x-ray), and had tolerated tube feeding for at least forty-eight hours. Subjects received Pulmocare as their enteral feeding mixture (calcium = 1.04 mg/mL; magnesium = 0.62 mg/mL; iron = 0.02 mg/mL). Subjects were excluded from the study for any of the following reasons: (1) history of hypersensitivity to quinolones; (2) pregnant or lactating women; (3) receipt of ciprofloxacin within one week of this study; (4) receipt of another investigational drug within 4 weeks prior to drug administration; (5) renal impairment indicated by creatinine greater than 3.0 mg/dL or creatinine clearance less than 40 mL/min.; (6) significant liver dysfunction defined as total bilrubin greater than 3 mg%; (7) granulocytopenia with granulocytes less than 1×10^6/L; (8) chronic inflammatory bowel disease; (9) history of pseudomembranous colitis; (10) concomitant administration of probenecid during the study. Prior approval for this protocol was obtained from the Human Investigation Committee, and written informed consent was obtained. Data regarding the subjects' age, weight, pre-existing medical conditions, and APACHE II score were tabulated (see Table I).

Sampling

Blood samples were collected for drug assay from existing arterial or central venous catheters before administration of the drug and at 0.25, 0.5, 0.75, 1.0, 1.25, 2.0, 4.0,

Table I. Demographics

Patient	Age	Sex	APACHE II	Vent days	CXR	WBC	Diagnosis	Surgical procedure
1	71	M	11	6	right infiltrate	12.7	S/P fall	N/A
2	46	M	8	9	left infiltrate	37.3	motor vehicle crash	tracheostomy
3	64	M	9	3	right infiltrate	11.0	respiratory failure	N/A
4	49	F	7	24	right infiltrate	15.9	motor vehicle crash	E-Lap
5	61	F	17	16	right infiltrate	12.7	pedestrian injury	N/A
6	34	M	5	15	right infiltrate	16.0	motor vehicle crash	ORIF, E-Lap
7	40	M	8	4	right infiltrate	12.1	stabbed to left flank	E-Lap
Mean	52.1		9.3	11		16.8		
Range	34 to 71		5 to 17	3 to 24		11 to 37.3		

E-Lap, Exploratory laparotomy; ORIF, open reduction and internal fixation of fraction, N/A, not applicable.

Table II. Pharmacokinetics

Patient	C_{max}	Dose 1	AUC_{0-12}	C_{max}	Dose 4	AUC_{0-12}
1	2.89	0.50	13.69	3.43	0.50	16.81
2	1.73	0.50	3.20	2.50	0.50	4.32
3	3.06	1.0	10.44	1.49	1.25	11.68
4	1.24	2.0	7.48	1.20	2.0	7.04
5	2.40	2.0	19.65	3.76	1.0	19.26
6	2.46	0.75	8.64	1.22	1.5	6.21
7	2.26	0.25	6.16	2.04	0.50	9.12
Mean	2.29	1.0	9.90	2.23	1.04	10.63
S.E.M.	0.24	0.27	2.05	0.39	0.22	2.11
Range	1.24 to 3.06	0.25 to 2.0	3.20 to 19.65	1.20 to 3.76	0.50 to 2.0	4.32 to 19.26

C_{max}, Maximum serum concentration (mg/L); T_{max}, time to reach maximum concentration (h); AUC_{0-12}, area under the serum concentration time curve from time 0 to time 12 h (mg.h/L).

12.0 h after doses one and four. Within 2 h of phlebotomy, samples were centifuged (20 min at 3200 rpm at 4°C), and the supernatant stored in glass vials at −70°C. Samples were shipped on dry ice to Bayer Corporation for drug assay.

Assay

Ciprofloxacin assay was performed by Bayer Corporation, Pharmaceutical Division, Clinical Pharmacology Laboratory. Serum concentrations were determined by high-performance liquid chromatography (Krol, Noe, & Beermann, 1986). The limit of sensitivity of this assay was 0.05 mg/L. The assay was linear over the range of 0.05–7.5 mg/L. The coefficient of variation associated with the intra-day precision and accuracy was less than 10% at all concentrations examined.

Statistical and pharmacokinetic analysis

Pharmacokinetic variables were determined using noncompartmental models. Maximum serum concentrations and time to maximum serum concentration were determined directly from the serum concentration time curve derived from the observed data following the first and last dose (steady state). The area under the curve values for each dose interval were determined by the log-linear trapezoidal method.

Results

The seven subjects had a mean APACHE II score of 9.3 (range 5–17) (see Table I). The maximum serum concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the curve for serum concentration versus time from $T = 0$–12 h (AUC_{0-12}) are listed in Table II for each subject. Values are means ± S.E.M.

When comparing mean data for all patients, pharmacokinetics for the first and fourth dose were similar (dose 1: $C_{max} = 2.29 \pm 0.24$ mg/L, $T_{max} = 1.0 \pm 0.27$ h, $AUC_{0-12} = 9.90 \pm 2.05$ mg.h/L; dose 4: $C_{max} = 2.23 \pm 0.39$ mg/L, $T_{max} = 1.04 \pm 0.22$ h, $AUC_{0-12} = 10.63 \pm 2.11$ mg.h/L). However, examination of the individual dose-response curves shows a moderate degree of variability.

Discussion

The principle finding of this study was that oral absorption of the 750 mg ciprofloxacin dose in critically ill patients was moderate, but variable. We chose to study enteric absorption of ciprofloxacin in mechanically ventilated patients with pneumonia because these individuals frequently have functioning gastrointestinal tracts and require antibiotic therapy. Pharmacokinetic analysis was performed on a heterogeneous group (in terms of patient age, type and severity of medical illnesses) which reflects the typical intensive care unit population.

Ciprofloxacin is well absorbed during enteral feeding in normal volunteers with a C_{max} of 2.92 ± 0.32 mg/L, and $AUC_{0-12} = 15.02 \pm 1.55$ mg.h/L which were similar to the findings noted in our critically ill population (Yuk *et al.*, 1989). Reduced gastrointestinal absorption of the drug with enteral feedings has been related to chelation by divalent cations (Mueller *et al.*, 1994). Ciprofloxacin absorption is diminished when patients are given Pulmocare when compared to Ensure or Osmolite, probably reflecting the fact that Pulmocare has twice the concentration of calcium and magnesium (Mueller *et al.*, 1994). In our study, serum ciprofloxacin concentrations after the initial study dose ($C_{max} = 2.29 \pm 0.24$ mg/L and $AUC_{0-12} = 9.9 \pm 2.05$ mg.h/L) were similar to those seen in normal volunteers after receiving a 500 mg oral dose ($C_{max} = 2.7 \pm 0.2$ mg/L and $AUC_{0-12} = 10.7 \pm 0.8$ mg.h/L) (Lettieri *et al.*, 1992). These serum levels were well above MICs for many important pathogenic bacteria. Chelation by divalent cations in the tube feeding solution probably contributed to the variability and reduction in drug absorption seen in our subjects. Use of alternative enteral feeding mixtures with lower concentrations of divalent cations or stopping tube feedings for a short period of time may result in improved drug absorption.

Acknowledgements

The authors wish to thank Dr Anita Shah, PhD for assistance with statistical analysis, and Bayer Corp., Pharmaceutical Division for providing grant support. Presented in part at the Surgical Infection Society meeting, Louisville, KT, USA, April 1995.

References

Bergan, T. (1988). Pharmacokinetics of fluorinated quinolones. In *The Quinolones* (Andriole, V. T., Ed.), pp. 119–54. Academic Press, London.

Cohn, S. M., Cohn, K. A., Rafferty, M. J., Smith, A. H., Degutis, L. C., Kowalsky, S. F. *et al.* (1995). Enteric absorption of ciprofloxacin during the immediate postoperative period. *Journal of Antimicrobial Chemotherapy* **36**, 717–21.

Fink, M. P., Snydman, D. R., Niederman, M. S., Leeper, K. V., Johnson, R. H., Heard, S. O. *et al.* (1994). Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrobial Agents and Chemotherapy* **38**, 547–57.

Khan, F. A. & Bair, R. (1989). Sequential intravenous-oral administration of ciprofloxacin *vs* ceftazidime in serious bacterial respiratory tract infection. *Chest* **96**, 528–37.

Krol, G. J., Noe, A. J. & Beermann, D. (1986). Liquid chromatographic analysis of ciprofloxacin and ciprofloxacin metabolites in body fluids. *Journal of Liquid Chromatography* **9**, 2897–919.

Lettieri, J. T., Rogge, M. C., Kaiser, L., Echols, R. M. & Heller, A. H. (1992). Pharmacokinetic profiles of ciprofloxacin after single intravenous and oral doses. *Antimicrobial Agents and Chemotherapy* **36**, 993–6.

Mueller, B. A., Brierton, D. G., Abel, S. R. & Bowman, L. (1994). Effect of enteral feeding with ensure on oral bioavailabilities of ofloxacin and ciprofloxacin. *Antimicrobial Agents and Chemotherapy* **38,** 2101–5.

Paladino, J. A., Sperry, H. E., Backes, J. M., Gelber, J. A., Serrianne, D. J., Cumbo, T. J. *et al.* (1991). Clinical and economic evaluation of oral ciprofloxacin after an abbreviated course of intravenous antibiotics. *American Journal of Medicine* **91,** 462–70.

Yuk, J. H., Nightingale, C. H., Sweeney, K. R., Quintiliani, R., Lettieri, J. T. & Frost, R. W. (1989). Relative bioavailability in healthy volunteers of ciprofloxacin administered through a nasogastric tube with and without enteral feeding. *Antimicrobial Agents and Chemotherapy* **33,** 118–20.

(*Received 21 December 1995; returned 21 March 1996; revised 9 April 1996; accepted 24 May 1996*)