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ENTERAL FEEDING AND FLUOROQUINOLONES

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ABSTRACT

"When the gut works, use it" is a common expression used to encourage the use of the enteral route for nutrition over the parenteral route in hospitalized patients. The same access device is often used to deliver both the enteral formula and medications without regard to the administration site (gastric versus small bowel). Changes in drug response as well as complications of drug administration may result from delivering enteral nutrition and medication together through the same tube. Currently, there is no standard of practice regarding the administration of specific medications when patients are receiving tube feeding, and if the feeding should be held for a period of time before and after drug administration. This report provides a general review regarding interactions between enteral feeding and the fluoroquinolones antibiotic class.

Key Words: Enteral feeding, Tube feeding, Fluoroquinolone, Ciprofloxacin

INTRODUCTION

Several issues must be considered with concurrent administration of oral fluoroquinolone antibiotics and enteral nutrition (EN), particularly continuous tube feeding, as incorrect administration methods may result in decreased drug effectiveness, increased adverse effects, drug-formula incompatibilities, or clogged feeding tubes. Unfortunately, there are few high quality studies evaluating fluoroquinolone interactions with continuous enteral nutrition. Several small studies have evaluated the influence of enteral feeding on fluoroquinolone pharmacokinetics with most focusing on ciprofloxacin; some studies support an interaction and some do not.

STUDIES SUPPORTING AN INTERACTION

In a study conducted by Mueller et al[1], 13 healthy adults were randomized to four oral treatments using a cross over design. The treatments were ofloxacin (400 mg) with water, ofloxacin (400mg) with Ensure, ciprofloxacin (750 mg) with water, and ciprofloxacin (750mg) with Ensure. A washout period of one week was used between each treatment. Water or Ensure were given as boluses every 30 minutes with a total of five doses; the study drugs were given with the second administration of water or Ensure. The area under the concentration time curve (AUC), the maximum concentration (C_{max}), and the absorption of both drugs were reduced by Ensure compared with water ($P< 0.01$). However, the relative bioavailability of ciprofloxacin (72%± 14%) was significantly less with Ensure than that of ofloxacin (90%±8.3%) ($P<0.005$).

Wright et al[2], performed an in vitro study using three quinolones mixed with five different mediums. Tablets of ciprofloxacin (500 mg), levofloxacin (500 mg), and ofloxacin (300 mg) were crushed and mixed with 240 ml of each medium: (1) water, (2) water plus calcium chloride (500 mg/L), (3) water plus magnesium chloride (200mg/L), (4) water plus calcium and magnesium, or (5) Ensure. Quinolone concentrations were measured at base line and at 0, 0.5, 2, 4, 8, and 24 hours. Ensure decreased the concentration of ciprofloxacin by 82.5%followed by levofloxacin with a 61.3% reduction and ofloxacin45.8% decrease. Conversely, there was no significant effect when each of the quinolones was mixed with the other mediums. However, the authors noted a relationship between the drug's degree of

lipophilicity and the percentage of drug lost with Ensure; the higher the lipophilicity (ofloxacin> levofloxacin > ciprofloxacin), the lower the percentage of drug loss.

Noer et al[3], using a randomized crossover design in 12 healthy volunteers, tested two different enteral formulas with water as a control. Ciprofloxacin (750 mg) tablets were crushed and given orally with A) water, B) Osmolite, or C) Pulmocare starting one hour before drug administration and every 30 minutes after for a total of five hours. C_{max} and AUC were significantly higher ($p < 0.01$) and ($p < 0.0001$), respectively, with water compared to enteral formulas. The C_{max} and AUC were similar for the two enteral formulas.

Healy et al[4], conducted a randomized crossover study on 26 hospitalized patients. The absorption and bioavailability of oral ciprofloxacin (500 mg) were evaluated when (1) given orally on empty stomach or with three oral doses of Sustical (240 ml given 8 h before, with, and 4 h after ciprofloxacin administration), (2) given with water through a gastrostomy or jejunostomy tube, or 3) given with Jevity as a continuous infusion (starting 6 hours before drug administration and continuing for 10 hours after). A 3-day washout period was used in each regimen. Enteral feedings, regardless of the route(oral, gastrostomy or jejunostomy),significantly reduced the C_{max} and the AUC of ciprofloxacin compared to the same route without feeding. The effect of C_{max} and AUC differed between routes.

STUDIES REFUTING AN INTERACTION

Yuk et al[5] studied 6 healthy volunteers using a randomized crossover design. Ciprofloxacin (750mg) was given orally, through a nasogastric tube (NG), or through an NG with a continuous infusion of Osmolite (6 hour infusion). A one-week washout was used between treatments. There were no statistically significant differences observed in the AUC, C_{max}, and time to peak concentration in any group. In a similar study including nasoduodenal (ND) administration, Yuk et al[6] reported that the absorption of ciprofloxacin with enteral feeding was greater when administered through a ND tube compared to a NG tube.

Burkhardtet al[7], studied the effect of concurrent enteral feeding on the pharmacokinetics and tolerability of moxifloxacin (400 mg) administered through the NG tube. Twelve healthy volunteers were enrolled and randomized to receive three separate treatment regimens using a crossover design with a one-week washout period between each treatment. Treatments consisted of oral moxifloxacin, moxifloxacin through a NG tube with water, and moxifloxacin through a NG tube with Isosource enteral feeding. C_{max} and AUC were slightly but not statistically significantly decreased with both NG regimes, and there were no significant differences observed in the time to reach C_{max} (t_{max}) with any treatment.

STUDIES WITH LOWER C_{MAX} AND ADEQUATE AUC

Two prospective studies evaluated ciprofloxacin administration with continuous enteral feeding through an NG tube in intensive care unit (ICU) patients. In the first study performed by Cohn et al[8], seven subjects received ciprofloxacin (750 mg) every 12 hours with Pulmocare as the EN formula. The authors noted that ciprofloxacin absorption was decreased with enteral feeding, however, the concentration remained above the minimum inhibitory concentration (MIC) for many pathogenic bacteria. The other study by Mimozet al[9], included 12 patients in a crossover design compared intravenous (IV) and NG administration of ciprofloxacin in patients receiving continuous EN. IV ciprofloxacin (400 mg twice daily) was initiated and changed to oral ciprofloxacin (750 mg twice daily) via NG tube after reaching a steady state concentration. The median C_{max} of ciprofloxacin was lower when given via NG compared to the IV route; however, the MIC and plasma AUC were similar between the two routes.

A small randomized crossover study by De Marie et al[10], also compared the administration of IV ciprofloxacin (400 mg twice daily) to the administration of oral ciprofloxacin (750 mg twice daily) with continuous enteral feeding (Nutrison or Nutrison E^{+}) through a NG or ND. The C_{max} and the AUC were evaluated in five critically ill ICU patients with severe gram-negative intra-abdominal infections. A period of 48-60 hours was used as a wash out phase. The C_{max} was lower after enteral administration than after IV administration 3.2μg/ml versus 6.8μg/ml respectively. Nevertheless, the AUC appeared to be equivalent for the two routes of administration.

DISCUSSION

Limitations to the available studies including small sample size, diverse study populations (healthy volunteers to ICU patients), varied EN delivery methods and routes, and different EN formula

characteristics, make it difficult to reach consistent conclusions regarding an interaction between fluoroquinolone antibiotics and enteral feeding.

This drug-nutrient interaction is often considered a class effect, however, the extent of the interaction appears to vary among the quinolones, ciprofloxacin being the greatest. The formation of non-absorbable chelates with divalent cations is often suggested as the mechanism responsible for reduced quinolone absorption characterized by diminished bioavailability and increased t_{max}. Frequently used enteral formulas contain varying amount of divalent cations, although with much lower concentrations compared to antacids as shown in Table 1. However, studies have not shown a correlation between cation content in EN formulas and reductions in C_{max} and AUC of fluoroquinolone antibiotics.[1,3,4] This suggests the possibility of other mechanisms of interaction. One in vitro study found that lipophilicity may explain differences in the degree of interaction between EN formulas and various quinolones.[2] Ciprofloxacin is hydrophilic and had the greatest percentage of loss in this study. In addition, ciprofloxacin is acid labile[6] and approximately 40% is absorbed from the duodenum[11], thus the route of administration may affect drug absorption. The study by Healy et al[4] noted that the reduction in C_{max} was less with gastric administration compared to jejunal administration.

The clinical significance of an interaction with the fluoroquinolones is largely dependent upon the extent to which the drug concentration is reduced below an effective concentration for the organism being treated (i.e. the MIC). The necessary MIC varies with different types and sites of infection. Several studies found that even though the C_{max} of quinolones decreased with concurrent EN, adequate plasma levels were maintained for treatment of various pathogens.[8, 9, 10]

There is no uniformly accepted practice regarding fluoroquinolone administration with EN. One recommendation is to hold EN at least 1 hour before and 2 hours after quinoloneadministration.[12] However, there is insufficient clinical evidence to support this recommendation, especially when applied to fluoroquinolones as a class. Moxifloxacin does not appear to have an interaction when administrated with EN.[7] In vitro, no significant reduction was seen when three different quinolones were mixed with calcium and magnesium containing solutions.[2]Other studies show different degrees of interaction with different fluoroquinolones.[1, 2] Another recommendation is that ciprofloxacin dosed through the NG tube with continuous feeding should be twice the IV dose (750 mg oral twice daily versus 400 mg IV twice daily).[9,10] Data to support this approach are also limited.

In conclusion, since the enteral feeding tube is increasingly used as a means of medication administration, as well as EN administration, well-designed studies are needed to clarify the exact mechanism and degree of loss for individual drugs within the quinolone class of antibiotics. Also, to confirm the validity of holding feedings, more evidence is warranted as this practice can result in inadequate administration of EN.

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Table 1: Mineral content in different enteral formulas and antacids

	Calcium	Magnesium	Zinc	Copper	Iron
Antacids					
Tums (mg)	420-1500				
Milk of magnesia (mg/ml)		400/5, 1200/15			
Enteral formulas (mg/L)					
Ensure	1266	422	24	2.1	19
Osmolite	760	305	18	1.6	14
Pulmocare	1060	425	24	2.2	19
Sustacal	1010	380	14.1	2	16.9
Jevity	910	305	18	1.6	14
Isosource	1072	428	32	2.2	19
Nutrison E^{+}	840	300	18	2.7	24

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