CASE REPORT

Ciprofloxacin: A Case of Multiple Interactions

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INTRODUCTION

Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic which has the potential to interact with a number of medications.[1] We report a case of suspected failure to respond to ciprofloxacin attributable to a drug interaction and discuss a number of potential interactions with ciprofloxacin.

CASE

A 63 year-old male presented to the emergency department with shortness of breath, cough and chest pain two days following discharge from the hospital's rehabilitation ward where he had been recovering from a right upper lobectomy for lung cancer. His stay had been prolonged and was complicated by aspiration pneumonia, acute respiratory distress syndrome and an upper GI bleed which had resulted in a cardiac arrest. The patient also had a history of coronary artery disease and a myocardial infarction two years earlier which had resulted in a ventricular aneurysm. Medications on admission included cisapride, diltiazem slow-release and nitroglycerin slow-release.

The emergency physician diagnosed the patient as having pneumonia with resultant hypoxemia causing anginal symptoms. Sputum was collected; oxygen therapy initiated; and he was ordered diltiazem slow-release 60 mg po bid, cisapride 5 mg po tid ac & hs, sucralfate 1 g po tid 1 h ac & hs, transdermal nitroglycerin 0.4 mg/hr for 12-14 hours daily, salbutamol 2.5-5 mg via nebulizer q2-4h prn, lorazepam 1 mg po hs prn, dimenhydrinate 50 mg po q6h prn and Maalox^{R} po prn. On hospital day two, methylprednisolone 125 mg IV q8h and ipratropium 500 mcg via nebulizer q4h were commenced and salbutamol was given regularly q4h. On day four, theophylline slow-release 300 mg po bid and cefuroxime 1 g IV q8h were added; the latter in response to a positive culture of Moraxella catarrhalis. On day eight, cephalexin 500 mg po qid replaced cefuroxime and weaning of the corticosteroid commenced. The dose of theophylline was also increased based on a low concentration to 400 mg po bid. On this regimen the serum concentration was subsequently reported to be 86 μmol/L (N55-110). On day 11, another sputum sample obtained in light of slow clinical improvement grew mixed bacteria including Pseudomonas species. Sensitivities were not performed. As a result of this, the patient was switched to ciprofloxacin 500 mg po bid. Two days after initiation of ciprofloxacin a pharmacist noted the potential ciprofloxacin-theophylline interaction and contacted the physician who lowered the dose of theophylline to 300 mg po bid and ordered a theophylline serum concentration to be drawn in three days. This was subsequently reported to be 44 μmol/L and theophylline was increased back to 400 mg po bid.

Despite continued ciprofloxacin therapy and chest physiotherapy, cough with purulent green sputum persisted. On day 24, two more potential interactions both of which reduce ciprofloxacin absorption were discovered; ciprofloxacin-sucralfate and ciprofloxacin-antacid. The pharmacist contacted the on-call physician to inform him of these interactions and subsequently the time of administration of the sucralfate and antacid were altered so as to avoid simultaneous administration with ciprofloxacin. As well, the nursing staff was informed of the issue and literature about the interactions was left on the patient's chart so that the regular physician would be aware of the potential problems. On day 26, the sucralfate was discontinued and the patient was given first ranitidine, then omeprazole. The patient's dyspepsia improved and very little antacid was requested thereafter.

A theophylline concentration ordered on day 26, two days after the

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sucralfate and antacid interactions were identified, was 101 μmol/L. On day 28, the patient's sputum was noted to be clear and ciprofloxacin was discontinued shortly thereafter. A repeat theophylline concentration drawn on day 33 was 93 μmol/L and the patient was discharged two days later.

DISCUSSION

The poor clinical response to ciprofloxacin between day 15 and 24 was attributed, in part, to the poor absorption of ciprofloxacin resulting from the concurrent use of both sucralfate and antacid. Throughout this period, the patient had purulent green sputum accompanied by cough. Four days after the interactions were identified and dealt with, the patient's sputum became clear. Theophylline serum concentrations provide further evidence that the absorption of ciprofloxacin had been compromised in this patient. A concentration of 44 μmol/L obtained while the patient was on ciprofloxacin, sucralfate, antacid, and theophylline 300 mg po bid increased to 101 μmol/L, only two days after the dose spacing of the sucralfate and antacid was instituted. The possibility does remain that the small increase in dose from 300 mg po bid to 400 mg po bid and/or possible nonlinear pharmacokinetics could have accounted for the change though this seems unlikely.[2]

This case involved several concomitantly administered drugs with known potential for interaction and it would appear that several of these interactions may have been involved. Theophylline clearance occurs by liver metabolism; more precisely by hydroxylation and N-demethylation carried out primarily by the iso-enzymes of the cytochrome P-450 system. It is thought that the interaction between ciprofloxacin and theophylline is caused by a competition between the 4-oxo metabolite of ciprofloxacin and theophylline for these iso-enzymes.[3] Other investigators believe that certain quinolones are potent selective inhibitors of specific cytochrome P-450 enzymes for theophylline metabolism.[4] The clinical significance of this interaction has been confirmed in a study of 33 patients receiving ciprofloxacin 750 mg po bid together with theophylline in which plasma theophylline concentrations increased in 20 patients and toxic concentrations were documented in ten of these patients.[5] While increases in theophylline concentrations seem to be greater in older patients and those on higher doses of ciprofloxacin, the extent of the interaction is quite variable between individuals.[6,7]

Sucralfate is a complex of aluminum hydroxide and sulfated sucrose. It is thought that aluminum ions released from the sucralfate molecule bind with ciprofloxacin decreasing its absorption.[8] One study demonstrated that sucralfate 1 g given concurrently with ciprofloxacin lead to an 88 percent decrease in ciprofloxacin's AUC.[9] Another study found that ciprofloxacin administered between two and six hours before sucralfate allowed sufficient time for ciprofloxacin absorption prior to the sucralfate dose and, thereby, minimized the chance of a significant interaction.[8] While this dose spacing would be difficult to achieve using sucralfate 1 g po qid, there is evidence that giving sucralfate 2 g po bid could be a viable, therapeutically equivalent alternative which was done in our case.[10]

The mechanism of the interaction between ciprofloxacin and the magnesium, aluminum, or calcium cations in antacids also appears to involve the formation of chelate complexes.[11] A 75-90 percent reduction in mean C_{max} has been reported when ciprofloxacin and magnesium-aluminum antacid preparations are concurrently administered.[12] However, as with sucralfate, dose spacing is an important variable in this interaction, as demonstrated by the fact that antacids administered six hours before or two hours after ciprofloxacin had little effect on serum concentration.[13]

There were two other interactions which had the potential to affect serum theophylline concentrations in our patient. Omeprazole has been reported to inhibit some cytochrome P-450 enzymes, although, one study suggested that significant metabolic inhibition is unlikely to occur at the doses used in clinical practice.[14,15] In addition, the administration of sucralfate may have lowered serum theophylline concentrations by affecting its bioavailability, although, a recent study concluded that the reduction in theophylline absorption was minimal and unlikely to be clinically important.[16] Nevertheless, one cannot dismiss the possibility of a clinically significant interaction involving either omeprazole or sucralfate and theophylline.

In their study of the combined use of sucralfate and ciprofloxacin, Van Slooten et al. suggest that the question of whether ciprofloxacin-cation interactions would result in treatment failures has not been adequately studied.[9] While most work on ciprofloxacin-antacid and ciprofloxacin-sucralfate interactions have involved healthy volunteers it would appear, based on this case, that these interactions may have clinical consequence.

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