CASE REPORT

Clinical Consequences of Quinolone-Theophylline Interactions

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INTRODUCTION

Several case reports regarding the potential of select quinolone antibiotics to interact with theophylline have appeared in the literature.[1-8] Evidence suggests that the elevations in theophylline concentrations that occur with concomitant fluoroquinolone therapy are due to an inhibitory effect upon cytochrome P-450-dependent microsomal metabolism of theophylline, although both a pharmacokinetic and a pharmacodynamic interaction is likely involved.[3,5,9,10] There is, to date, little information on the morbidity associated with this interaction. We report four cases of this interaction and offer guidelines for the use of these agents.

CASE 1

A 77 year-old woman was admitted with dehydration secondary to severe nausea and vomiting. Six weeks earlier she underwent a left knee arthroplasty complicated by infection, requiring irrigation and debridement two weeks later. At that time, she was started on ciprofloxacin 750 mg po bid. Approximately one week later she started to complain of nausea which continued to worsen; by ten days she was vomiting about ten times a day. She denied any fever or chills.

Her past medical history included asthma for the past 20 years, congestive heart failure, gastric ulcer, and arthritis. She had a previous cholecystectomy and incisional hernia repair. She did not smoke or drink alcohol. Her medications on admission were theophylline sustained release 300 mg po bid, ciprofloxacin 750 mg po bid, furosemide 40 mg po daily, salbutamol 200 mcg inhaled as needed, budesonide 400 mcg inhaled twice daily, and acetaminophen 325 mg -650 mg po q4h prn.

On examination, her blood pressure was 130/80 mmHg both lying and sitting; heart rate was 105 (lying) and 110 (sitting) beats per minute and was irregularly irregular. Respiratory rate was 16 per minute and temperature 37.6°C. The rest of the physical examination was unremarkable except for pitting edema to the mid-calf.

Routine chemistries were within normal limits with the exception of a hemoglobin at 103 g/L, platelets at 535 $x10^9$/L, serum bicarbonate at 31 mmol/L and serum potassium at 2.6 mmol/L. A chest X-ray showed a hiatus hernia and mild hyperinflation with flattening of the hemidiaphragms. The electrocardiogram showed atrial fibrillation.

At this time, it was felt that her nausea, vomiting and possibly her atrial fibrillation were due to theophylline toxicity secondary to a drug interaction with the ciprofloxacin. The theophylline was stopped and she was rehydrated with intravenous fluids and potassium chloride. A theophylline serum concentration was drawn and was subsequently reported as 160 µmol/L (normal range: 55-110). Over the next 48 hours, her appetite returned to normal and she converted back to normal sinus rhythm. She was discharged home on ciprofloxacin, salbutamol, and budesonide.

CASE 2

A 93 year-old woman was found at her nursing home lying on the floor having generalized tonic-clonic movements which lasted for approximately five minutes. When the ambulance arrived she was unresponsive and mildly cyanotic.

Her past medical history consisted of chronic obstructive pulmonary disease (COPD), glaucoma, left cataract surgery, and thyroidectomy in 1960. Her current medications included pilocarpine 4% one drop in left eye twice daily, beclomethasone 100 mcg inhaled qid, amitriptyline 10 mg po qid, levothyroxine 50 mcg po

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daily, furosemide 40 mg po bid, potassium chloride 20 mmol po tid, digoxin 0.25 mg alternating with 0.125 mg po daily, oxazepam 10 mg po hs prn, theophylline sustained release 300 mg po bid, cyanocobalamin 100 mcg IM monthly, and a recent one-week course of norfloxacin 400 mg po bid.

On examination, her blood pressure was 180/80 mmHg, heart rate 87 beats per minute, and respiratory rate 20 per minute. She was afebrile, alert, and oriented. Her chest was clear to auscultation, with a normal S_1, S_2 and no S_3 or S_4; however, there was a grade 2/6 systolic ejection murmur. Neurological exam was normal except for the left cataract and mild left facial droop. The rest of the physical examination was unremarkable.

Routine chemistries were reported as being in the normal range with the exception of potassium at 3.3 mmol/L. Capillary gases showed PO_2 58, pH 7.43, PCO_2 39, bicarbonate 26, with an oxygen saturation of 90%; these values were similar to her previous capillary gases. An electrocardiogram showed atrial fibrillation, left ventricular hypertrophy and an old anteroseptal infarct. A chest X-ray showed cardiomegaly and vasculature redistribution. A theophylline serum concentration was drawn and subsequently reported to be 183 µmol/L (normal range: 55-110). Digoxin serum concentration was 1.1 nmol/L (normal range: 0.6-2.6).

The patient was admitted to hospital with a diagnosis of theophylline toxicity felt to be secondary to a drug interaction with norfloxacin. Theophylline therapy was stopped. A CT scan of her head was done to rule out a CNS cause for her seizure. It showed slight leukoaraiosis above the trigone and old right and left lacunar infarcts in the basal ganglia. Her improvement was gradual and her hospital stay was prolonged due to several complications. Several weeks later she was discharged home on her regular medications excluding theophylline. At the time of discharge she was in normal sinus rhythm.

CASE 3

A 76 year-old woman with a remote history of seizures following a stroke was found in a nursing home unresponsive with tonic-clonic activity that lasted about 10 minutes. When the ambulance arrived she had another generalized seizure, lasting about five minutes, and then a focal seizure in the emergency department involving her left arm and left face. She had been discharged from another hospital one day previously after a two-week stay for a left lower lobe pneumonia treated with cotrimoxazole. During her stay, her phenytoin dosage had been adjusted and she had been maintained on theophylline sustained release 200 mg once daily during her stay. Upon discharge she was commenced on ciprofloxacin 500 mg po bid. On returning to the nursing home her previous dose of theophylline sustained release 200 mg po tid was resumed.

Past medical history included two previous strokes in 1983 and 1989. Each of these events was complicated by seizures: however, no seizures had occurred since 1989. She also had a history of chronic obstructive pulmonary disease, non-insulin dependent diabetes, hypertension, renal calculi, and a left knee hemiarthroplasty. Her medications on admission were ciprofloxacin 500 mg po bid, theophylline sustained release 200 mg po tid, phenytoin 100 mg po tid, glyburide 5 mg po daily, salbutamol 200 mcg inhaled qid prn, and beclomethasone 100 mcg inhaled bid. She was reportedly "allergic" to penicillin, sulphonamides, and meperidine.

On examination, her blood pressure was 130/70 mmHg, heart rate of 120 beats per minute, respiratory rate of 30 per minute and she was afebrile. She was unarousable with no spontaneous eye opening and no response to movement. Her pupils were equal in size at 2 mm and reactive. Doll's-eye and vestibulo-bulbar responses were intact. Her chest was clear to auscultation, with normal heart sounds and no extra sounds or murmurs. The rest of the physical examination was unremarkable.

Investigations showed the WBC to be elevated at 14.8 $x10^9$/L with a hemoglobin of 145 g/L, and platelets of 698 $x10^9$/L. The rest of the routine chemistries were normal except for glucose at 13.6 mmol/L. Serum magnesium, phosphate, and calcium were normal. No serum theophylline concentration was obtained. Electrocardiogram showed normal sinus rhythm with left ventricular hypertrophy. Chest X-ray showed diffuse osteopenia, multiple bilateral rib fractures and slight blunting of the posterior costophrenic angles.

Theophylline therapy was stopped and her antibiotic switched initially to erythromycin, then doxycycline. A CT scan of the head was done to rule out a new CNS event. It showed an old infarct in the right occipital lobe in the watershed region. Over the next 24 hours the patient became fully alert and orientated with no further seizure activity.

She was discharged home six weeks after admission on her previous medications, excluding theophylline, as well as vitamin D and calcium supplements. Her seizure on admission was felt to be secondary to the concomitant administration of theophylline and ciprofloxacin as well as an increased dosage of theophylline.

CASE 4

A 78 year-old man was admitted with severe nausea, vomiting, and diarrhea. Approximately one week earlier he had been started on tetracycline for an exacerbation of COPD. Several days later, in response to urinary symptoms, he was switched to norfloxacin. About five days later he began to experience nausea, vomiting, and diarrhea.

Past medical history included long-standing COPD, benign prostatic

hypertrophy for which he had a transurethral resection in 1990, previous hemorrhoid surgery, and a tonsillectomy. His medications prior to admission were theophylline sustained release 300 mg po tid, salbutamol 2 mg po tid, salbutamol inhaler 200 mcg qid prn and salbutamol nebulizer solution 2.5 mg q4h prn, bethanechol 10 mg po tid, and naproxen 250 mg po bid. This theophylline dose had not changed in the past year.

On examination his blood pressure was 130/80 mmHg with a postural drop of 20 mmHg, heart rate of 112 beats per minute and a respiratory rate of 24 per minute. He was afebrile. His heart sounds were quiet with no extra heart sounds or murmur heard. He had decreased breath sounds bilaterally with crackles heard at the right base. His abdomen was soft and bowel sounds were present. The rest of the physical examination was unremarkable. Routine chemistries revealed an elevated urea of 16.4 mmol/L and creatinine of 160 mmol/L. The WBC was 6.1 x 10^9/L and hemoglobin was elevated at 185 g/L. The electrocardiogram showed sinus tachycardia, left bundle branch block and right atrial enlargement. His chest X-ray showed marked hyperinflation consistent with COPD. A serum theophylline concentration was reported to be 159 µmol/L (normal range: 55-110).

The patient was admitted with a diagnosis of theophylline toxicity felt to be secondary to a drug interaction with norfloxacin. His theophylline was stopped and he received intravenous rehydration. Unfortunately, he went into acute pulmonary edema the next day, then respiratory failure requiring intubation. Two days later he was extubated. An echocardiogram was done to determine the cause of his acute pulmonary edema. It was consistent with ischemic heart disease showing previous myocardial infarctions involving at least two separate territories. He was restarted on his theophylline and discharged home eight days after admission on salbutamol, ipratropium and theophylline SR 200 mg tid.

DISCUSSION

The potential for interaction between quinolone antibiotics and theophylline has been extensively described.[1-4] However, few reports have commented on the clinical significance of this interaction.[5-8] Our four cases show that morbidity necessitating hospitalization may occur as a result of the interaction.

In two cases the quinolone involved was ciprofloxacin; the other two involved norfloxacin. All our patients were elderly, exemplifying both the population most likely to receive these drugs and also the group at greatest risk for toxicity from them. The major toxicities associated with the cases were gastrointestinal, cardiovascular, and neurological toxicity, notably seizures. The two patients who developed seizures had a history of CNS disease – previous history of seizures in one case and, in the other, previous stroke detected only upon CT scan during this hospitalization. Ciprofloxacin when administered alone has been associated with seizure activity in part attributable to its ability to antagonize GABA.[9] Furthermore, there appears to be an additive pharmacodynamic interaction when quinolones are combined with theophylline.[10] A recent case[5] and a recent review by Shalansky et al [11] supports that both a pharmacokinetic and pharmacodynamic interaction may contribute to the risk of seizure. The rapid onset of seizures in our third case would also support that pharmacodynamic interaction occurs.

In all of the cases in which a theophylline serum concentration was measured, concentrations above the therapeutic range were reported. In one case, no theophylline concentration was obtained and, hence, elevated theophylline concentrations could not be confirmed despite a presentation compatible with theophylline toxicity. Failure to obtain a theophylline serum concentration likely reflects the diminishing use of theophylline and with it, a reduced familiarity with the agent.

Studies, usually in younger normal volunteers, indicate that the risk of interaction varies with the quinolone used.[2] For example, enoxacin has a greater effect on theophylline clearance than does ciprofloxacin which in turn has a greater effect on theophylline clearance than does norfloxacin.[2] The reported clearance change with norfloxacin is small, on the order of 15%.[12,13] Despite this small change in clearance, a recent meta-analysis has suggested that the interaction between norfloxacin and theophylline may be significant.[3] Our two cases would support this.

In a study reported by Hamilton et al,[6] the incidence of admissions to hospital due to theophylline interactions was low with only one of 59 courses of theophylline and ciprofloxacin resulting in hospitalization. Data on the ages of those patients were not given, but it is noteworthy that the one patient who was hospitalized was 80 years of age. Our experience suggests that the interaction may be more problematic in that that this interaction accounted for 0.64% (4 of 626) of admissions to our service over approximately a one-year period. While these scenarios are not directly comparable, in view of the diminishing utilization of theophylline, this would appear to be an interaction with potential morbidity, particularly in the elderly. Furthermore, although no fatalities occurred, a considerable patient and health care cost was incurred due to residual morbidity and prolonged hospital stay.

In view of these findings, we would suggest that the combination be avoided. Whenever possible, a non-interacting antibiotic should be selected. When not possible, discontinuation of theophylline should be

considered, while recognizing that elderly COPD patients may derive benefit from this drug and patients should be monitored for evidence of decompensation.[14] If both drugs are essential, the dose of theophylline should be monitored using serum drug concentrations with the aim of not exceeding low normal theophylline concentrations (30-55 µmol/L, 6-10 mg/L). Theophylline or both drugs should be discontinued in the event of toxicity.

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