Case Report

Clarithromycin-Warfarin Interaction Resulting in an Elevated INR

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INTRODUCTION

Warfarin, a vitamin K antagonist, is commonly used to treat thrombosis.[1] Drug interactions involving warfarin have the potential to be serious. Once a desired therapeutic response is achieved, it is important to maintain that efficacy. The addition or deletion of certain medications from an individual's drug profile can have a pronounced effect on the anticoagulant effect of warfarin. The following case illustrates the effect of initiating clarithromycin in an individual recently started on warfarin.

CASE

A 68 year-old male with a history of COPD, diabetes mellitus (Type II), and gout was admitted to hospital with complaints of chest pain, shortness of breath, and a feeling of "chest tightness". He also complained of lower right quadrant pain that radiated to the right leg. The admitting diagnosis included pneumonia, exacerbation of COPD, and possible DVT. The patient weighed 90.4 kg and was 172 cm in height. He had a stated allergy to penicillin. Upon admission a venosonogram of his right leg and a chest x-ray were performed.

The venosonogram showed an extensive DVT within his right popliteal vein. The chest x-ray noted infiltrates/pulmonary edema in the left midlung zone of the chest. While pneumonia was suspected, pulmonary embolism secondary to the DVT could not be ruled out. Heparin IV and ceftriaxone 1 g IV every 24 hours was initiated. Lab values reported on admission were as follows: WBC - 10.4 x $10,^9$ segmented neutrophils - 78%, Bands - 0%, INR - 1.0, aPTT-22.9 sec., creatinine - 230 umol/l, calculated creatinine clearance (CrCl) - 27-29 ml/min.(Cockroft-Gault Equation), urea - 13.6 mmol/l, electrolytes - WNL. Medications on admission included metformin 500 mg BID, levothyroxine 0.2 mg QD, omperazole 20 mg BID, enalapril 2.5 mg BID, potassium chloride 8 mEq BID, hydrochlorothiazide 50 mg QD, furosemide 80 mg QD, and allopurinol 200 mg QD.

Heparin was dosed intuitively to reach a therapeutic aPTT of 2 times the control which was achieved by day 2. Warfarin therapy was instituted on day 3 with a starting dose of 10 mg. Heparin was stopped on day 8 and warfarin continued at a dose of 5 mg per daily. Measured INR at this point was 2.5. On day 9, ceftriaxone was discontinued. Warfarin dosing continued at 4 - 5 mg per day resulting in an INR range of 2.3 - 2.7(Days 10 - 13). On day 13, clarithromycin 500 mg twice daily was started for suspected worsening of chest infection/pneumonia. On day 14, ceftriaxone 1 g every 36 hours was added to the drug regimen. The INR on day 14 was 3.6 thus no warfarin was given. Days 15 and 16 saw the INR increase dramatically to 7.1 and 9.3, respectively, in spite of the withholding of warfarin. The INR slowly decreased until on day 20 the INR was measured to be 2.4. At this point, warfarin 2 mg was reintroduced. Clarithromycin was subsequently stopped on day 21 while ceftriaxone was stopped on day 23. From day 21 to day 27 (date of discharge) the patient received warfarin 3 mg daily with INRs measured ranging from 2.0 - 2.4. On day 27, the patient was discharged on warfarin 3 mg daily. The only other changes made to this patient's drug regimen was the deletion of omperazole and hydrochlorothiazide (day 4 and 14, respectively) and the addition of nitroglycerin patch 0.4 mg/h and cisapride (day 2 and day 25, respectively). Due to the timing of these changes they did not have any bearing on the outcome of this case. Table I illustrates pertinent medication dosing and laboratory patterns of the patient over the 27 days of hospitalization.

DISCUSSION

Warfarin has the propensity to interact with a number of different medications via a number of different mechanisms. Inhibition of vitamin K co-factors, lack of dietary vitamin K, disease states, enzyme induction, and protein binding can effect the pharmacodynamics of warfarin. Medications, such as some

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cephalosporin antibiotics, can inherently exhibit an anticoagulant effect thus exaggerating the anticoagulant effect of warfarin. Two mechanisms have been proposed to cause this effect. A vitamin K dependant mechanism and suppression of platelet activity are thought to be the 2 ways in which cephalosporins (and beta lactams) cause hypoprothrombinemia.[2,3,4,6] A N-methyltetrathiozole (nMTT) ring attached at position 3 of the cephem nucleus is thought to account for an increase in INR through inhibition of vitamin K dependant co-factors responsible for hemostasis.[2,3] Ceftriaxone contains an aminothiozole side chain at position 3 rather than the nMTT side chain. It is postulated that these 2 side chains have similar effects on INR.[2] Common physiologic parameters seen in patients at risk for hypoprothrombinemia from cephalosporins include malnourishment, decreased gastrointestinal function, liver and /or renal insufficiency.[3,6] However, as the data illustrate, there was no apparent effect on the INR by ceftriaxone when used as a single agent during the first course of therapy (Table I).

During the second course of antibiotic therapy, clarithromycin and ceftriaxone were prescribed. Shortly after the initiation of clarithromycin, the INR began to increase dramatically (Table I). Macrolides (especially erythromycin) are known to decrease warfarin clearance by inhibiting cytochrome P-450.[1,8,9,10] Cytochrome P-450 is a general term used to describe a family of isozymes (mixed-function monooxygenases) that are responsible for the phase I (oxidative) metabolism of a wide number of compounds.[9,10,11] Warfarin (a mixture of 2 isomer, R and S) is specifically metabolized by isozymes of the CYP3, CYP1, CYP2 families.[9,10] Erythromycin inhibits a number of isozymes including CYP3 and CYP1. Structurally different from erythromycin, clarithromycin is a hydrophobic macrolide and contains a non-hindered N- dimethyl amino group. These structural changes make clarithromycin's impact on cytochrome P- 450 less pronounced.[8,12,13] However, clarithromycin is known to inhibit the isozyme family CYP3 (Specifically CYP3A4).[9,10,13] The CYP3 family of isozymes are most abundant in the liver and medications metabolized by this family of isozymes are especially subject to adverse interactions when co-administered.[10]

Table I. Pertinent Drug Administration and Laboratory Results of Patient During Hospitalization.

Day of Hospitalization	INR	Warfarin Dosage (Mg)	Clarithromycin 500 mg BID		Ceftriaxone 1g q 24h
			0800	1800	1000
1		0			x
2		0			x
3	1.0	0			x
4		10			x
5	1.1	10			x
6	1.3	10			x
7	1.8	7			x
8	2.5	5			x
9	3.0	3			x
10	2.7	4			
11	2.4	5			
12	2.3	5			
13	2.7	5	x	x	q 36 h
14	3.6	0	x	x	x(1000)
15	7.1	0	x	x	x(2200)
16	9.3	0	x	x	
17	5.9	0	x	x	x(1000)
18	5.1	0	x	x	x(2200)
19	3.7	0	x	x	
20	2.4	2	x	x	x(1000)
21	2.0	3			x(2200)
22	2.1	3			
23	2.2	3			x(1000)
24	2.3	3			
25		3			
26	2.4	3			
27	Discharged Home				

Clarithromycin is extensively metabolized in the liver by cytochrome P-450. Seven metabolites have been shown to be formed including 14-hydroxyclarithromycin which exhibits antibacterial activity. Clarithromycin exhibits non-linear dose dependant pharmacokinetics. As the dose increases, the serum concentration increases disproportionately. This is seen after multiple doses.[8,14] While clarithromycin is extensively metabolized in the liver, studies have shown that clarithromycin's and the active metabolite's (14-OH clarithromycin) half-life increases as renal function declines.[8,13,14] When clarithromycin was evaluated in patients with creatinine clearances <30 ml/min; C_{max} , AUC, and $t_{1/2}$ were all increased compared to a group who had creatinine clearances of >80 ml/min.[8] This patient's creatinine clearance as noted was <30 ml/min. Due to his compromised renal function , one would expect clarithromycin to have an extended $t_{1/2}$, increased AUC, and elevated C_{max} thus potentiating its effect on the cytochrome P-450 enzyme system.

Warfarin is highly protein bound (approximately 97%).[14] Medications that are highly protein bound can displace warfarin from its protein binding; the clinical significance of these types of drug interactions is unsubstantiated. Ceftriaxone is 58 - 96% protein bound depending upon dose.[15] Clarithromycin has been reported to have protein binding in a range between 42 - 72% at usual therapeutic concentrations.[14] In addition, protein binding of clarithromycin and the 14-OH metabolite tend to decrease with increasing serum drug concentrations.[14] Due to the extended interval of ceftriaxone (every 36 hours vs 24 hours) and the probable increased drug serum concentrations of clarithromycin, one could expect

that the protein binding of these 2 drugs would be at the lower end of their respective ranges. The role that this particular mechanism may have played in contributing to the increased INR is undetermined.

Other reasons need to be explored before implicating a drug/drug interaction as the cause of the elevated INR. Sepsis has the potential to decrease liver metabolism thus increasing the effects of warfarin.[16] While this patient was queried as having pneumonia, he never exhibited classical signs or symptoms. Temperature remained within normal limits and WBC count decreased after the admitting blood work. The patient continued to complain of chest discomfort and a repeat chest x-ray on day 12 showed no change from admission. Due to the patients history of COPD, antibiotic therapy was re-instituted. The chest discomfort was felt to be most likely attributed to the COPD or possibly pulmonary embolus. Decreased dietary intake of Vitamin K can also attribute to an exaggerated anticoagulant effect from warfarin.[1,14] While in hospital, the patient received a 1400 calorie/day(no added salt) diet which was similar to what he had been used to. Since sepsis was not a factor and the patients diet remained somewhat stable, neither of these components probably played a role in the elevated INR that was seen.

In conclusion, the monograph for clarithromycin makes reference to a warfarin drug interaction as being not reported in clinical trials but being observed with macrolides.[1] It documents a caution when using warfarin and macrolides together but does not specifically implicate clarithromycin. In the presence of renal dysfunction, a resultant increase in clarithromycin serum drug concentration can result in a heightened inhibitory effect on the cytochrome P-450 enzyme system. Also given that clarithromycin inhibits the same family of isozymes (CYP3) that is responsible, in part, for the metabolism of warfarin, it is plausible that clarithromycin could increase the anticoagulant effect of warfarin. Whether or not the active metabolite of clarithromycin plays any role in this interaction is not clear. The role of ceftriaxone in this interaction should not be discounted as it may have contributed to the increased INR. However, it did not have an effect on the INR when used singularly, thus, it is difficult to implicate it in this case. Due to the renal dysfunction exhibited in this patient and the non-linear pharmacokinetics of clarithromycin, a lower dose may have avoided such a significant reaction by avoiding excessive serum drug concentrations. Caution should be used when administering clarithromycin and warfarin to individuals who exhibit compromised renal function, and additional INR determinations should be carried out when adding this or any other drug to the regimen of a patient on warfarin.

REFERENCES

1. Gillis MC,ed. Compendium of Pharmaceuticals and Specialties. 31st ed. Toronto. CK Productions.1996.
2. Fekety FR. Safety of parenteral third generation cephalosporins. *Am J Med* 1990;88 (4A):38-44S.
3. Mandell GL, Petri WA. Antimicrobial Agents. In: Hardman JG, Limbird LE, Molinoff PG. eds.The Pharmacological Basis of Therapeutics. New York, NY.McGraw Hill;1996:1073-101.
4. Nakahara M. Effects of antibiotics on platelet thromboplastic function and thrombin activity. *J Med* 1978;9:433-43.
5. Tatro D. ed. Facts and Comparisons:Drug Interaction Facts. St. Louis: Facts and Comparisons Inc., 1996.
6. Sattler FR, Weitekamp MA, Ballard JO. Potential bleeding with the NEW Beta-lactam antibiotics. *Ann Intern Med* 1986;105:924-36.
7. Beam TR, Jr. Ceftriaxone: A Beta-lactamase stable, broad spectrum cephalosporin with an extended half-life. *Pharmacotherapy* 1985;5:237-53.
8. Piscitelli SC, Danzinger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics.*Clinical Pharmacy* 1992;11:137-52.
9. Bennett D. Something about the cytochrome system.[letter] Pharmacist Letter.1996;12:26.
10. Tatro D. Cytochrome P-450 enzyme drug interactions.[letter] Pharmacist Letter. 1996;12:26.
11. Buck ML. The Cytochrome P-450 enzyme system and It's effect on drug metabolism. *Ped Pharmacotherapy,* Children's Medical Center, University of Virginia. 1997;3:1-6.
12 Neu HC. The Development of macrolides: clarithromycin in perspective. *J Antimic Chem* 1991;27 (supp A):1-9S.
13. Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinetic* 1992;23:106-31.
14. McEvoy GK,ed. American Hospital Formulary Service Drug Information. Bethesda. American Society of Hospital-System Pharmacists Inc.1997.
15. Blumer J. Pharmacokinetics of ceftriaxone. In: Current clinical management of infections:Part II. *Hospital Practice* 1991;26(Supp 5):7-13S.
16. Sleager, J. Shock syndrome related to sepsis. In: Wyngaarden JB, Smith LH, eds. Cecil Textbook of Medicine. Toronto:WB Saunders Co; 1988:1538-9.