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Ciprofloxacin–Warfarin Coagulopathy: A Case Series

Robert J. Ellis,[1]* Matthew S. Mayo,[2] and David M. Bodensteiner[1]

[1]Division of Hematology/Oncology, University of Kansas Medical Center, Kansas City, Kansas
[2]Director of Biostatistics of the Kansas Cancer Institute, University of Kansas Medical Center, Kansas City, Kansas

Ciprofloxacin, when given to patients previously anticoagulated with warfarin, can occasionally cause an exaggerated hypoprothombinemic response and bleeding diatheses. Two such cases encountered at our institution are presented and data is combined with 64 cases reported to the Food and Drug Administration's (FDA) Spontaneous Reporting System (SRS) database, which included all cases reported from 1987 through 1997. Of 66 total cases the median age was 72 (range 36–94). The mean time to detection of the coagulopathy following the ciprofloxacin challenge was 5.5 days ($n = 50$). Hospitalization was reported in 15 cases, bleeding in 25 cases, and death in one case. The median prothrombin time (PT) and International Normalized Ratio (INR) was 38.0 ($n = 13$) and 10.0 ($n = 23$), respectively. The mean number of medications taken was 6.5 ($n = 45$). The mean time to correction was significantly shorter between the treated (2.5 days) and the untreated (4.0 days) groups ($P < 0.008$). The ciprofloxacin–warfarin coagulopathy occurred most commonly in patients in their seventh decade and in those who require polypharmacy. Active treatment of the coagulopathy results in more rapid resolution than observation alone. Clinicians should be aware of the potential bleeding complications that can occur with the ciprofloxacin–warfarin drug–drug interaction. Am. J. Hematol. 63:28–31, 2000.

Key words: ciprofloxacin; warfarin; coagulopathy; drug–drug interaction; bleeding; prothrombin time

INTRODUCTION

Hemorrhagic events from hypoprothrombinemia attributed to ciprofloxacin–warfarin drug interactions have been reported in sufficient number to warrant concern over prescribing this drug combination [1–7]. Eight cases were reported in the literature soon after the introduction of ciprofloxacin in 1987, and many more cases have been reported to the Food and Drug Administration's Adverse Drug Reporting system, now Spontaneous Reporting System (SRS). These reports prompted the FDA to make recommendations about product labeling, and have inspired investigators to conduct small prospective studies of the ciprofloxacin–warfarin combination [8–10]. These trials did not reproduce hypoprothrombinemia or bleeding in study populations. Because of the infrequency of the phenomenon, and lack of reproducibility, those with an interest in studying the interaction are left with gathering information from case reports either from the literature or various data bases.

We present two cases encountered at our institution where ciprofloxacin–warfarin interaction was suspected of causing exaggerated hypoprothrombinemia which led to clinical bleeding. We then report and summarize descriptive data which was reported to the FDA's SRS from 1987 through 1997.

CASE 1

A 50-year-old female with rheumatoid arthritis and previous stroke, was chronically anticoagulated with warfarin for antiphospholipid antibody syndrome. Five days prior to seeking medical attention her PT and INR were known to be 20.8 and 3.0, respectively. Her other medications included wafarin, prednisone, cyclosporine, lisinopril, methotrexate, diltiazem, folate, and conjugated estrogens.

She presented to her primary care physician with void-

*Correspondence to: Robert J. Ellis MD, University of Kansas Medical Center, Division of Hematology, 1417 Bell, 3901 Rainbow, Kansas City, KS 66160-7233. E-mail: rellis2@kumc.edu

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ing complaints and pyuria on urinalysis, and was prescribed oral ciprofloxacin, 500 mg twice daily. Two days later she returned to an emergency room with new complaints of lethargy, nausea, and frontal headache as well as continued complaints of dysuria. During the first hospital day she became obtunded. A noncontrast computed tomography scan of the head revealed the presence of bilateral subdural hematomas. She was transferred to our hospital for neurosurgical evaluation.

At our institution her PT was found to be 36.5 s and her INR was 8.8. Following the administration of 10 mg of vitamin K, her INR fell to 1.0 within 12 h. She was taken to the operating room where burr holes and clot evacuation was accomplished. Post operatively her mental status and physical functioning returned to baseline. Following the removal of her surgical drains, anticoagulation was resumed with low-dose continuous infusion heparin while oral warfarin was reinstituted. On hospital day 18 she was discharged on low-molecular weight heparin and warfarin in good condition. The INR was 2.4 six days later, and it remained in the therapeutic range thereafter on her previous dose of warfarin.

CASE 2

A 56-year-old male who was chronically anticoagulated with warfarin because of prosthetic mechanical aortic and mitral valves, presented to the hospital with intractable brisk epistaxis and a PT of 81.2 s and an INR of 53.9. Four days prior ciprofloxacin, 750 mg p.o. BID had been prescribed for scrotal cellulitis. His INR was known to be 3.5 seven days prior to his presentation. Other medications were warfarin, amiodarone, folate, prednisone, diltiazem, lisinopril, ranitidine, furosemide, digoxin, relafen, and methotrexate. Prior to the administration of ciprofloxacin no changes had been made in either medication or dosing.

Treatment was initiated with vitamin K 6 mg, FFP 12 units, nasal packing, and oxymetazoline nasal spray. The bleeding slowed over 2 days, and the INR corrected to 2.1. Transfusion with 8 units of packed red blood cells were required to maintain an adequate hemoglobin. He then required an incision and drainage procedure of a scrotal abscess. Oozing of blood from the wound postoperatively prompted administration of 4 additional milligrams of vitamin K. On the third postoperative day the INR was 1.1 and his bleeding symptoms had ceased. Heparin was infused empirically to prevent thrombosis of his mechanical heart valves. On hospital day 9 he underwent secondary closure of his surgical wound without significant postoperative bleeding. Warfarin was then reinstituted without further bleeding complications. He was discharged on hospital day 18 with an INR of 2.2 on his previous dose of warfarin.

METHODS

The FDA's SRS is a computerized database which contains case reports of adverse drug reactions that occur during the postmarketing period [1]. In April 1997, this database was queried and a listing of all cases in which a fluoroquinilone and warfarin were used concomitantly was generated regardless of the suspected reaction. Spontaneous Reporting System forms which contained a description of bleeding events or alterations in measurements of coagulation tests (PT or INR) were identified. Clinical data was extracted from the forms which fulfilled previously defined criteria for causation of drug–drug interactions [12]. The data extracted included whether or not anticoagulation existed in steady state concentrations prior to the ciprofloxacin challenge, time in days from the ciprofloxacin challenge to the discovery of the elevated PT or INR, values for elevated PT and INR at discovery, and whether the coagulopathy was actively treated or the patient simply observed. Other data collected included age, gender, the four most common concurrent medications, bleeding events, hospitalization, and medical problem lists. A statistical comparison between the actively treated and observation groups was performed.

RESULTS

Sixty-four cases from the SRS and our 2 cases contained descriptions of bleeding events, ciprofloxacin, warfarin, and laboratory coagulation parameters. Reported age ranged from 36 to 94 with a median of 72 ($n = 56$). Gender was identified for 33 females and 27 males ($n = 60$). The median time to detection of the coagulopathy after Ciprofloxacin was administered was 5.5 days ($n = 50$). The median PT and INR at the time of detection were 38.0 ($n = 43$) and 10.0 ($n = 23$), respectively. Hospitalization was reported in 15 cases, bleeding in 25 cases and death in one case. The coagulopathy was actively treated in 24 cases. Treatment consisted of vitamin K alone in 16, FFP alone in 3, vitamin K and FFP in 4, and vitamin K, FFP, and Amicar in one. In 12 cases the warfarin and ciprofloxacin was simply held. In 30 cases, no mention of treatment was made. The mean time for correction of the INR was 2.5 days in the patients actively treated compared to 4.0 days in those in whom the ciprofloxacin and warfarin were stopped. ($P < 0.008$, Fisher's exact test) The mean number of medications taken by the 56 patients in whom concurrent drugs were reported was 6.5. The four most frequent concurrent medications by class were; a diuretic ($n = 21$), digoxin ($n = 20$), a calcium channel blocker ($n = 11$), and a histamine H_2 receptor antagonist ($n = 8$).

TABLE I. Prospective Fluoroquinilone–Warfarin Trials

Study	Study design	*n*	Patients	Drug	Coagulation effect
Verho [14]	Single arm	7	HV[a]	Ofloxacin	None
Toon [15]	Randomized crossover[b]	6	HV	Enoxacin	(*R*) Warfarin isomer
Rocci [16]	Randomized crossover	10	HV	Norfloxacin	None
Wyld [17]	Single arm	10	HV	Temafloxacin	None
Rindone [8]	Single arm	9	Warfarin clinic	Ciprofloxacin	None
Bianco [9]	Placebo-controlled[c]	16	Warfarin clinic	Ciprofloxacin	None
Israel [10]	Placebo-controlled[d]	36	Warfarin clinic	Ciprofloxacin	(*R*) Warfarin isomer

[a]Healthy volunteer.
[b]Randomized, two-way crossover design.
[c]Randomized, double-blind, placebo-controlled trial.
[d]Randomized, double-blind, placebo-controlled, multicenter trial.

DISCUSSION

Hemorrhagic morbidity from the hypoprothrombinemic response apparently induced by administering ciprofloxacin to patients previously anticoagulated with warfarin is an uncommon albeit well described event. Warfarin exists as a racemic mixture of (R) and (S) enantiomers, and directly exerts part of its anticoagulant effect via these isomers [13]. A prospective study which measured the isomers of warfarin demonstrated elevations in the (R) isomer when a ciprofloxacin was administered in the study setting [10]. Prospective trials which combined ciprofloxacin and other flouroquinilones with warfarin have failed to demonstrate a significant increment in prothrombin times or INRs [8–10,14–17]. However these studies have been criticized because of lack of randomization [9,14,17], the use of young healthy volunteers as study subjects [14–17], and small sample sizes [8,14–17] (Table I). The lack of evidence that these drugs directly affect prothrombin times and INRs in anticoagulated patients has led some authors to conclude that ciprofloxacin and flouroquinilones do not produce a clinically significant reaction, despite compelling evidence to the contrary [1–7].

The cohort of patients described herein includes 64 cases retrieved from the FDA's SRS database and 2 additional cases encountered at our institution. This descriptive data suggests that the drug–drug interaction occurs most commonly in patients who require polypharmacy for the management of multiple medical problems and those in their seventh decade of life. On the basis of the reported events, the mean time to correction in patients available for analysis was 2.5 days in the treated group versus 4.0 days in the group in whom ciprofloxacin was simply held and the patients were observed. The biochemical mechanisms underlying the ciprofloxacin—warfarin interaction are unknown. Numerous hypotheses have been proposed in the literature, and these are broadly categorized as those affecting protein binding [18], interference with drug metabolism, or those affecting elimination kinetics of warfarin [19]. However, experimental data to support any of these theories is lacking.

The frequency of the ciprofloxacin–warfarin reaction is impossible to estimate. In lieu of large prospective studies, which are impractical and possibly unethical, the ideal setting for studying the ciprofloxacin–warfarin interaction may be anticoagulation clinics [10,20]. A prospective case–control study conducted on patients enrolled in a anticoagulation clinic measured factors that were associated with INRs greater than 6.0 [20]. Among 93 cases where high INRs were identified, 20 were reported as receiving a new medication. Of these 20, four were flouroquinilones (ciprofloxacin = 3 and ofloxacin = 1). In this same study, acetaminophen ingestion was independently associated in a dose-dependent manner with having an INR greater than 6.0 (P for trend <0.001) and was reported as a concomitant medication in 52 of 93 cases examined. In our group, acetaminophen was listed in only 2 of 45 cases where data on concurrent medications were reported.

The accumulation and summary of clinical data from series of cases is useful in helping to identify when, and in whom monitoring may be useful. Our data suggests that it may be prudent to check INRs in older individuals taking, multiple medications within 4–5 days following the initiation of ciprofloxacin. Clinicians should remain vigilant for the potential exaggerated hypoprothrombinemic effect which may ensue when this drug is given to patients anticoagulated with warfarin. Aggressive efforts to analyze descriptive data on groups of patients must be undertaken if the full benefit of the voluminous data collected in adverse drug reaction databases is to be realized.

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