

Potential Glucosamine-Warfarin Interaction Resulting in Increased International Normalized Ratio: Case Report and Review of the Literature and MedWatch Database

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We describe a 71-year-old man who had received warfarin 7.5 mg/day for 5 years for atrial fibrillation, which had maintained his international normalized ratio (INR) within a narrow range of 2.5–3.2. During this 5-year period, he had also been treating himself with the supplement glucosamine hydrochloride 500 mg–chondroitin sulfate 400 mg twice/day for arthritis. The patient then increased his dosage of glucosamine to 1500 mg and chondroitin to 1200 mg twice/day; his INR previous to this change was 2.3. Approximately 3 weeks later, his INR increased to 3.9. His supplement dosage was reduced to glucosamine 750 mg–chondroitin 600 mg/day; a repeat INR done 16 days later was 4.7. The supplement was then stopped, and his warfarin schedule was changed to 7.5 mg every other day alternating with 3.75 mg every other day. Sixteen days later, his INR was 2.6. This case report suggests that a potential interaction exists between warfarin and glucosamine that is associated with an increase in the INR. We therefore performed a pharmacovigilance survey of spontaneously reported adverse events in warfarin-treated patients concomitantly exposed to glucosamine, glucosamine–chondroitin sulfate, or chondroitin sulfate and present a literature review of this apparent drug-drug interaction. Using the United States Food and Drug Administration (FDA) MedWatch database, 20 reports of glucosamine or glucosamine–chondroitin sulfate use with warfarin associated with altered coagulation (manifested by increased INR, or increased bleeding or bruising) were identified. In some cases, a decrease in the supplement dosage was followed by a return of the INR to the previous therapeutic range. Similarly, a decrease in warfarin dosage was followed by a decrease in INR in one patient who received long-term warfarin therapy. One report described an intraventricular bleed and subdural hematoma, which resulted in a persistent vegetative state. The World Health Organization (WHO) adverse drug reactions database documented 21 spontaneous reports of increased INR associated with glucosamine use, 17 of which resolved when glucosamine was stopped. We located one published case report of concomitant use of glucosamine–chondroitin sulfate potentiating the effect of warfarin. In aggregate, the reports from the FDA and WHO, the published case report, and our case report suggest that the use of warfarin and glucosamine may lead to an increased INR. Patients should be advised that the use of the two products may cause an increase in INR, and they should inform their health care provider if they consume glucosamine. More information is necessary to define this interaction.

Key Words: glucosamine, warfarin, chondroitin sulfate, international normalized ratio, INR, bleeding.

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Glucosamine hydrochloride or sulfate, either alone or together with chondroitin sulfate, is used as a supplement for joint health. A 2002 study of 32,000 individuals found that 14.9% of people 18 years or older had consumed glucosamine supplements during the past 12 months.¹ Yearly sales of the supplement in 2006 were estimated to be more than 40 million units (standardized to 100-count bottles) in the United States.² Glucosamine is added to foods and beverages. On March 7, 2007, an enhanced orange juice product containing glucosamine hydrochloride 750 mg/240 ml (8-oz serving) became available in the United States. Glucosamine is approved as a prescription drug for the treatment of osteoarthritis by regulatory agencies in Europe.

Glucosamine is often consumed by the elderly, a group often prescribed warfarin for the prevention of thromboembolic complications associated with atrial fibrillation. The number of dispensed outpatient prescriptions for warfarin increased from 21 million in 1998 to nearly 31 million in 2004.³ Atrial fibrillation is a growing public health problem, and the number of persons with the diagnosis is projected to triple by 2050 as a result of the aging population.⁴

Warfarin has a narrow therapeutic index and is susceptible to interactions with other drugs, foods, and a substantial number of dietary supplements and agents.⁵ These can cause a previously well-controlled international normalized ratio (INR) to increase above the upper limit of the therapeutic range. There is no mention in the warfarin package insert or the *Physicians' Desk Reference*, two commonly used resources by physicians, of a potential warfarin-glucosamine interaction. One literature report of a probable warfarin-glucosamine interaction, published in 2004,⁶ is mentioned in Micromedex, a drug-interaction software package; and by Clinical Pharmacology Gold Standard Inc., a developer of drug information databases,

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software, and clinical information solutions used by some pharmacies to obtain drug interaction reports. Warfarin-glucosamine drug interaction data are limited, and as such, physicians and patients may not be aware of the potential for an increase in the INR value.

In this article, we document a case of a probable adverse event to warfarin associated with the concomitant use of glucosamine-chondroitin sulfate, we identify spontaneous reports of adverse events of warfarin and glucosamine-chondroitin sulfate interaction compiled by the United States Food and Drug Administration (FDA) MedWatch adverse drug event surveillance system, and we review the literature for reports of a warfarin and glucosamine-chondroitin sulfate interaction.

Case Report

A 71-year-old man had been receiving warfarin 7.5 mg/day for 5 years for atrial fibrillation; this dosage had maintained his INR value within the narrow range of 2.5–3.2. During this 5-year period, he had also been treating himself with glucosamine hydrochloride 500 mg-chondroitin sulfate 400 mg twice/day for arthritis. His medical history was also significant for hypertension and hypercholesterolemia. The dosages of his concomitant drugs had remained stable for the previous 2 years and included ezetimibe 10 mg-simvastatin 40 mg/day, amlodipine besylate 5–10 mg/day, lisinopril 20 mg-hydrochlorothiazide 25 mg/day, aspirin 162.5 mg/day, vitamin C 1000 mg twice/day, vitamin E 400 IU every other day, and fish oil capsules 1000 IU twice/day.

The patient decided to increase his dosage of glucosamine to 1500 mg and chondroitin to 1200 mg twice/day; his INR previous to this change was 2.3. At a routine follow-up visit almost 3 weeks later, his INR value had increased to 3.9. He reported no changes in his diet, although he did report that he had been taking the glucosamine-chondroitin supplement. The patient had the supplement with him, and the ingredients listed on the bottle were examined. The glucosamine hydrochloride ingredients were from shellfish, crab, and crayfish (location of the harvest not mentioned); the chondroitin sulfate sodium ingredients were croscarmellose sodium, microcrystalline cellulose, silicon dioxide, magnesium stearate, stearic acid from soy, sodium lauryl sulfate, hydroxypropylmethylcellulose, polyethylene glycol, and carnauba wax.

The patient was instructed to reduce the supplement dosage to glucosamine 750 mg–chondroitin 600 mg/day. A repeat INR performed 16 days later was 4.7. The patient was then instructed to stop taking the supplement, and his warfarin schedule was changed from 7.5 mg/day to 7.5 mg every other day alternating with 3.75 mg every other day. Sixteen days later, his INR was 2.6.

MedWatch Case Reports

Through the MedWatch program, the FDA compiles and maintains an adverse drug event report database for drugs and biologic products used by humans. Reports from manufacturers associated with their products are required by law, whereas reports from health care professionals and consumers are voluntary. The reports are collected into an electronic database referred to as the Adverse Events Reporting System (AERS).

We searched the AERS on June 6, 2007, for reports of interactions between warfarin (sodium warfarin, Coumadin) and glucosamine (glucosamine hydrochloride, glucosamine sulfate–chondroitin sulfate). The search was followed by a manual review of each report to exclude duplicate reports. Individual MedWatch reports vary in their comprehensiveness. We also identified a World Health Organization–adverse drug reaction (WHO-ADR) report on glucosamine and glucosamine–chondroitin sulfate administration in warfarin-treated patients.⁷

A search of the MedWatch AERS database using the interaction search format identified 81 nonduplicated U.S. cases that reported the search term warfarin with either glucosamine (hydrochloride or sulfate)–chondroitin sulfate combination or glucosamine or chondroitin sulfate separately. Possible alternative etiologies, insufficient data, and confounding factors such as use of multiple drugs suspected of interacting with warfarin occurred in 61 of 81 cases. These cases were not reviewed further. The remainder of the MedWatch reports we evaluated varied considerably in completeness of information provided, possibly reflecting, among other things, differences between reports by consumers and those from health care professionals.

Table 1 summarizes the 20 voluntary, spontaneous cases reported to MedWatch and was constructed to be similar to the table in the WHO report,⁷ which listed relevant cases in which glucosamine and warfarin were suspected of

interacting or glucosamine was classified as concomitant. The MedWatch reports indicated concomitant use of warfarin and glucosamine either alone (four cases) or in combination with chondroitin sulfate (15 cases), or warfarin reportedly used with chondroitin sulfate only (one case [case no. 1], in which the consumer mentioned chondroitin). Most of the reports were from consumers and did not provide a listing of other potential interactive factors affecting the INR. Concomitant drugs listed for the 20 cases were checked for reports of elevated INR values. Case nos. 3, 4, and 12 listed drugs used by the patients for which there were reports of elevated INR values.

Among the 20 cases, there were 10 men and 9 women, with 1 case report providing no information regarding sex. Ages ranged from 33–89 years (median age 62 yrs). The duration of exposure to the dietary supplements before the documented onset of the increase in INR value was noted infrequently in the reports. The times to onset of the increase in the INR and outcomes after adjusting the dosage of the supplement or warfarin were not consistently delineated in the spontaneous reports. One case description mentioned that a decrease in the dosage of glucosamine–chondroitin sulfate was associated with a return of the elevated INR to the therapeutic range established previously during long-term warfarin therapy. A decrease in warfarin dosage resulted in a decreased INR to the therapeutic range in the patient identified as case no. 16, another user of long-time warfarin therapy. The dosage of warfarin was reduced in two patients with elevated INRs (case nos. 18 and 20), but no outcome data were reported.

No deaths were reported. Serious cases were reported and resulted in patient hospitalization. Five patients (case nos. 2, 4, 6, 7, and 8) were hospitalized for various bleeding complications such as gastrointestinal bleeding (case no. 2), which required transfusion and administration of vitamin K; hematomas (case nos. 7 and 11); one subdural hematoma resulting in a persistent vegetative state (case no. 7); hematuria (case no. 4); and an intraventricular bleed (case no. 8). Excessive bruising or hematoma was reported in six cases (case nos. 5, 6, 10, 11, 12, and 14) and prolonged bleeding in two others (case nos. 9 and 13).

Literature Search

We performed a search of the MEDLINE,

Table 1. 20 Voluntary MedWatch Reports of Cases Involving Potential Interactions of Warfarin and Glucosamine with or without Chondroitin Sulfate

Case No.	Age (yrs)/ Sex	INR Relative to Glucosamine Use		Outcomes and Other Relevant Information
		Before	During	
1	67/M	2.9	6.6	Long-term warfarin use for 2 yrs; chondroitin sulfate ^a 1500 mg/day ^b ; chondroitin sulfate stopped, in 2 days INR was 2.1
2	89/M	NR	↑	Glucosamine–chondroitin sulfate used; gastrointestinal bleeding, treated with vitamin K and packed red blood cells
3	NR/F	2.7	3.4	Glucosamine–chondroitin sulfate used; patient took celecoxib concomitantly with glucosamine–chondroitin and warfarin
4	70/M	2.2	5.4	Glucosamine–chondroitin sulfate used; hematuria; chondroitin sulfate used concomitantly with rofecoxib in past without incident
5	NR/M	NR	↑	Warfarin used for 8 yrs; increased bruising when glucosamine–chondroitin sulfate used
6	33/M	NR	5.0	Long-term warfarin use; epistaxis, rectal bleeding, bruising, and hospitalization after glucosamine–chondroitin sulfate use
7	77/F	NR	4.7	Subdural hematoma and permanent vegetative state; glucosamine ^a used
8	57/F	NR	4.1	Intraventricular bleed due to a potential warfarin and glucosamine–chondroitin sulfate interaction
9	NR/M	NR	NR	Consumer noted prolonged bleeding with warfarin and glucosamine–chondroitin sulfate
10	66/F	NR	4.0	Warfarin used for 7 yrs; consumer noted hematoma; glucosamine–chondroitin sulfate used; patient also took fluoxetine; anecdotal reports of increased INR
11	70/F	2.1	2.4	Consumer reported INR “started bouncing,” and she had purple toes and bruised easily (hematoma); glucosamine–chondroitin sulfate used
12	47/F	3.1	5.6	Glucosamine–chondroitin sulfate used; pharmacist reported that patient bruised easily; she also took paroxetine and propranolol
13	61/F	NR	NR	Consumer reported that she bled profusely; glucosamine–chondroitin sulfate used
14	50/F	NR	4.5	Warfarin used for > 10 ys; bruises; glucosamine–chondroitin sulfate used
15	70/M	1.3	4.0	Consumer reported elevation in her father's INR; glucosamine ^a used
16	76/M	NR	4.1	Warfarin used for 2 yrs; decreased warfarin dosage resulted in decreased INR to therapeutic range; glucosamine ^a used
17	69/M	NR	3.9	Consumer reported elevated INR; glucosamine–chondroitin sulfate used
18	67/M	2–3	4.5	Consumer reported increase in INR; dosage of warfarin decreased (INR result NR); glucosamine–chondroitin sulfate used
19	NR/NR	NR	↑	Nurse reported that patient had increased INR with warfarin and glucosamine ^a use
20	58/F	NR	4.8	Consumer reported port wine stains; warfarin dose decreased (outcome data NR); glucosamine–chondroitin sulfate used

INR = international normalized ratio; NR = not reported; ↑ = increased.

^aThe accuracy of the consumer's report of using either glucosamine alone or chondroitin sulfate alone, rather than the commonly used combination product of glucosamine (hydrochloride or sulfate)–chondroitin sulfate, could not be verified.

^bHis dosage of 1500 mg/day is the dosage for the combination tablet, with 1200 mg/day the dosage for chondroitin sulfate; this intimates a possible inadequate recall by the consumer of the actual product used.

Embase, and International Pharmaceutical Abstracts databases (January 1, 1950–June 12, 2007). The literature search located one case report, similar in several respects to our case, of a 69-year-old man with a diagnosis of atrial fibrillation.⁶ He had been stabilized with warfarin 47.5 mg/week, with INR values in the range of 2.0–3.0 for 4 months. Within 4 weeks of consuming glucosamine hydrochloride 3000 mg/day and chondroitin sulfate 2400 mg/day, his INR increased to 4.52. His weekly warfarin dose was changed to 40 mg, and he continued to take

glucosamine hydrochloride–chondroitin sulfate at an unknown dosage. His INR decreased to 2.15 within 2 weeks and was maintained in the target range of 2.0–3.0 for 3 months with no further warfarin dosage adjustments. He reported no changes in his diet or drug regimen, which consisted of fexofenadine taken during the allergy season, oral butalbital caffeine–acetaminophen as needed for headaches, and oral sumatriptan taken occasionally for migraines. There was no indication when the last dose of butalbital, a cytochrome P450 (CYP) 2C9 inducer, was taken.

Discussion

To our knowledge, this is the first comprehensive report in the United States suggesting that glucosamine or glucosamine combined with chondroitin sulfate might potentiate the anticoagulant effects of warfarin.

We identified a total of 43 unique cases (our case report, 20 from MedWatch, 21 from WHO, and one published case report) in which an increased INR response was reported to occur with use of warfarin plus glucosamine or glucosamine–chondroitin sulfate (or mention of chondroitin sulfate only). This is a relatively small number given the popularity of glucosamine supplementation and the number of prescriptions written for warfarin. However, underreporting can be presumed; the fraction of adverse drug event reports (for all drugs) received by the FDA has been estimated at 1–10%.⁸ Furthermore, a study commissioned by the FDA estimated that the FDA is notified of less than 1% of all adverse events associated with dietary supplements (A. Walker, unpublished observations, 2000).

We found that the spontaneous case reports from the WHO-ADR database, in contrast to the reports from the United States, were noteworthy for their substantive clinical detail, including confirmation of prior stability of warfarin dosing, exclusion of confounding factors, and evidence of a return of the INR value to the therapeutic range after glucosamine was stopped.⁷ An explanation for the differences in warfarin–glucosamine drug interaction case reporting may be due in part to the fact that medicinal glucosamine is a prescription drug in European countries. As such, manufacturers are obligated to report adverse events; thus, this may influence the quality and completeness of the reports. Most of the spontaneous reports that we evaluated from the MedWatch surveillance system were from consumers and did not provide consistently systematic detail in a uniform fashion.

The cases compiled by the WHO surveillance system suggested that concomitant use of glucosamine potentiates the anticoagulant effects of warfarin.⁷ To further understand this, it is helpful to mention some findings from the WHO report. The dietary supplement is defined as glucosamine (either as hydrochloride or the sulfate salt) rather than glucosamine–chondroitin sulfate in most of these foreign reports; this is likely to be accurate because glucosamine is

written as a prescription drug in European countries. Eleven of the patients who had been taking long-term warfarin therapy had a stable INR when they started taking glucosamine. The event was detected in 3 weeks in eight patients and within 1–3 months in five patients. Chondroitin sulfate use, apparently without glucosamine, was reported in only two of the 21 cases. It is not known whether or not these reports were substantiated with respect to reporting accuracy or whether or not the report of chondroitin use by the individual was simply a truncated version of a glucosamine–chondroitin sulfate product and related to patient or health care provider recall and proclivity for brevity of words.

Twenty-one reports cited an increased warfarin effect on the INR. The event resolved in 81% of the 21 individuals when glucosamine was stopped. The adverse reaction reappeared in one patient who was exposed a second time to glucosamine–chondroitin sulfate. Others apparently were not rechallenged. Possible alternative etiologies for the increased INR and confounding factors (e.g., drugs) were not addressed in this brief WHO report.

Our case demonstrated a temporal association between an increase in the INR value and concomitant use of glucosamine hydrochloride–chondroitin sulfate and warfarin. A tripling of the dose of the dietary supplement was followed by an elevation in the INR value in this patient with a previous stable INR response. Although a transient increase in the INR occurred (rather than the expected decrease) when the dose of the supplement was subsequently reduced, this is not incompatible with the ultimate return to baseline INR. A delayed return to baseline could be the outcome of numerous factors, alone or in combination, such as changes in diet including alcohol use, environment, physical state, changes in hepatic blood flow, and clearance of warfarin or altered gastrointestinal motility or as-yet-unidentified metabolic effects of glucosamine. The patient had been taking simvastatin for 8 years followed by a combination product during the last 2 years without any increase in the INR value, thus minimizing this drug as a possible alternative source for the increased INR response. It is important to note that these factors were not evaluated in the spontaneous reports, making it difficult to define or support the interaction.

Changes in daily vitamin K intake may contribute to marked variations in the INR in patients receiving warfarin, with potentially

serious adverse outcomes.⁹ Information on dietary vitamin K intake was not provided in any of the case reports that we examined. Vitamin K is a group name for vitamin K₁ (or phyloquinone) and vitamin K₂ (or menaquinone). Both forms of vitamin K contribute to tissue status. Vitamin K₁ is found in green leafy plants, and vitamin K₂ is found in very low concentrations in milk, fermented products, and liver. Vitamin K₁ and vitamin K₂ are lipophilic and differ in their bioavailability. Menaquinones have a more widespread distribution, whereas phyloquinones are preferentially accumulated in the liver.¹⁰ Vitamin K₂ is synthesized by bacteria in the intestinal tract in significant concentrations and may have the potential to interfere with oral anticoagulant treatment. The long-chain menaquinones, which are extremely lipophilic, may not be easily mobilized. The contribution of vitamin K₂ to the overall vitamin K pool is not clearly defined. However, the hepatic turnover of the menaquinones is slower (longer half-life) and the biologic response longer, thus it may serve as a more constant source of vitamin K than phyloquinone.¹⁰ This difference in the half-life times in the circulation may account for some of the variation in the INR during warfarin use, for example, in the case presentation of our patient. A well-rounded “mixed diet” is likely the dietary requirement of vitamin K. We do not know whether or not glucosamine exposure affects vitamin K₂ synthesis in the intestinal tract. Drugs such as some antibiotics have been associated with a reduction in hepatic menaquinone concentration, lending credence to the contention that a reduction in gut flora responsible for production leads to reduced hepatic stores of menaquinone.

The quality of the diet has the potential to vary the form and concentration of vitamin K in different tissues, which may impact the efficiency of progressive carboxylation needed for the production of a limited number of proteins, including prothrombin. The liver receives the dietary vitamin K absorbed from the gut and the carboxylation reaction occurs in the endoplasmic reticulum of the cell (Figure 1).^{11, 12} Vitamin K is a cofactor of a carboxylation reaction accomplished by the enzyme γ -glutamyl carboxylase by which the glutamic acid residues, weak chelators of calcium, are modified to form γ -carboxyglutamate residues, which are much stronger calcium chelators, and to generate active clotting factors such as prothrombin. The vitamin K epoxide must be recycled to vitamin K before it

can be reused, a reaction catalyzed by the enzyme vitamin K epoxide reductase, a process that is inhibited by warfarin. Theoretically, potentiation of the warfarin effect by glucosamine administration could be a result of competing with either the vitamin K-dependent carboxylation step or by competing with calcium binding sites on the prothrombin precursor containing glutamic acid and/or the prothrombin containing the γ -carboxyglutamate residue that results from the vitamin K-dependent carboxylation reaction. Reduction of the number of γ -carboxyglutamate residues on the prothrombin molecule from the normal complement of 10 or 13 to nine residues results in a 30% reduction of coagulant activity, whereas a reduction to less than six residues results in a loss of more than 95% of coagulant activity.¹³ Increased levels of glucosamine may result in increased competition with the calcium binding sites on both the prothrombin precursor containing glutamic acid and γ -carboxyglutamate, thus decreasing prothrombin's binding of calcium, a crucial step in clotting. The combination of polymorphisms within the vitamin K epoxide reductase complex and CYP2C9 that affect warfarin pharmacodynamics and pharmacokinetics, respectively, may explain a large portion

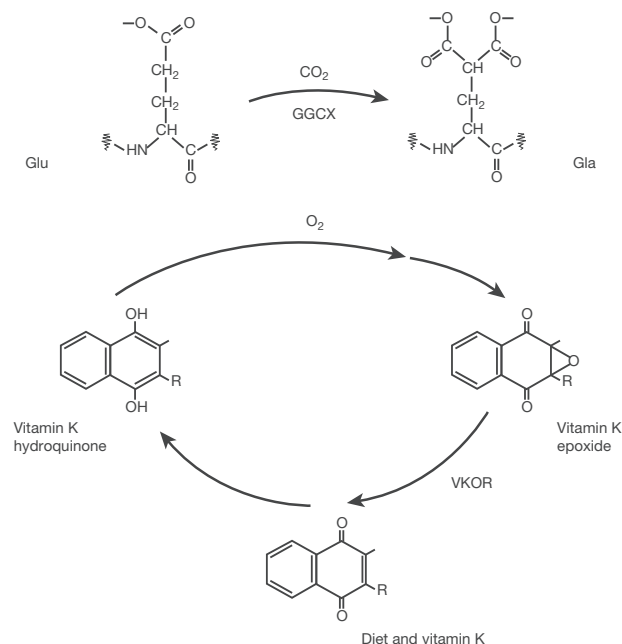


Figure 1. The vitamin K cycle. Glu = prothrombin precursor containing glutamic acid; Gla = a prothrombin containing γ -carboxyglutamic acid residue; GGCX = γ -glutamyl carboxylase; VKOR = vitamin K epoxide reductase; R = carbon side chains.

of the variability in the warfarin response.¹⁴

We documented several cases of INR values above the narrow therapeutic range of 2.0–3.0 in persons exposed to glucosamine and warfarin often accompanied by reports of bleeding, although we could not exclude other factors known to be associated with altered hemostasis. The variety of clinical and environmental factors that modulate warfarin dosage requirements were examined and included in the description of our 71-year-old patient and, to a certain extent, in the other published case report, but were absent for the most part from the other cases.

The intensity of anticoagulation, which is measured by the INR, is strongly associated with an increase in the risk for major hemorrhage during warfarin therapy. The annual cumulative rate of adverse hemorrhagic events in patients with a recorded INR of 5.0 or greater is reported to be 16.6%.¹⁵ In fact, the first 90 days of warfarin use in patients aged 80 years or older with an INR of 4.0 or higher is associated with a 3-fold increased risk of major hemorrhage.¹⁵

Numerous endogenous and exogenous factors alone or in combination may be responsible for increased INR response. Endogenous factors include blood dyscrasias, cancer, chronic heart failure, hepatic disorders, and vitamin K deficiency. Changes in daily vitamin K intake may contribute to marked variations in the INR coagulation index in patients treated with warfarin, with potentially serious adverse outcomes.⁹ Even though these factors were not mentioned in any of the cases we reviewed, it does not preclude the fact that one or more of these factors may have been present but simply not reported. Exogenous factors are numerous and include specific drugs, some foods, and botanicals. Frequent drug interactions have been encountered when warfarin is coadministered with specific drugs. There are at least 132 drugs that interact with warfarin and may be responsible for increased INR response; these are listed in the package insert for warfarin.¹⁶ Glucosamine is a naturally occurring 6-carbon amino monosaccharide and a constituent of the disaccharide repeating unit of the glycoaminoglycans heparin sulfate, keratin sulfate, and hyaluronic acid present on animal cell surfaces and in the extracellular matrix. At physiologic pH, the amino group in glucosamine is protonated, resulting in a positive charge.

Any alteration in the uptake or metabolism of warfarin (e.g., reduced clearance, elimination) or vitamin K by glucosamine would be expected to influence the INR value. Warfarin, a weak organic

acid, circulates bound to plasma proteins (97–99%), mostly to albumin. Protein binding can provide a reservoir of bound warfarin, which can replenish some of the warfarin that is lost to metabolism and excretion. Competition between drugs for binding sites on plasma proteins can lead to large increases in the free concentration of warfarin, producing unexpected toxicity. Therefore, warfarin intensity can change when albumin levels decrease and potential binding sites disappear. The number of binding sites for drug molecules per albumin molecule is usually much smaller than the total number of charged groups (e.g., $-\text{NH}_2^+$) and the affinity for these few sites is greater than for common counter ions such as Na^+ interacting at the anionic groups and Cl^- at the cationic sites.¹⁷ Warfarin rapidly accumulates in the liver where it is metabolized by CYP isoenzymes. From the metabolic profile of glucosamine, it is unlikely that the potentiating effect of glucosamine on warfarin is a result of altered warfarin pharmacokinetics. Likewise, there is no evidence that glucosamine influences the absorption of warfarin from the intestine or decreases its metabolic clearance through blockade of the CYP isoenzymes.

Glucosamine is absorbed from the small intestine. A significant amount is catabolized by first-pass metabolism in the liver and finally to carbon dioxide, water, and urea.¹⁸ The oral bioavailability after first-pass metabolism is 26%.¹⁸ Glucosamine is not protein bound but rather incorporates into plasma proteins, primarily globulins.¹⁸ The glucosamine that is not metabolized or incorporated into plasma proteins is excreted in the urine.

The pharmacodynamics of warfarin are affected by many factors that can influence its anticoagulant effect. For instance, individuals exposed to long-term warfarin therapy are sensitive to fluctuating levels of dietary vitamin K, which is obtained predominantly from plant material.¹⁹ Various drugs augment the anticoagulant effect of warfarin by inhibiting the cyclic interconversion of vitamin K.²⁰ Patients receiving warfarin who have unstable control of anticoagulation have a significantly lower intake of dietary vitamin K compared with their stable counterparts.²¹ It is not known whether glucosamine use results in vitamin K deficiencies by altering vitamin K absorption from food sources or influencing the intestinal flora that is responsible for vitamin K₂ production. Vitamin K₁ absorption by the ileum and colon is by a passive diffusion mechanism that is modified by bile salt concentration, pH,

and unsaturated fatty acids. Vitamin K₁ is rapidly metabolized by the liver and is depleted in poor diets. A lowered vitamin K status may predispose to hypoprothrombinemia.

Finally, it is crucial that we mention the potential significance of glucosamine added to other products. Glucosamine is often taken at a dosage of 1500 mg/day (500 mg 3 times/day) for several months. Recently, beverages such as orange juice have been marketed as enhanced juices. These 1.75-liter bottles contain 750 mg/240 ml. This amount may not be significant in a patient receiving warfarin, although more information is necessary to clearly define any potential dose-related event between glucosamine and warfarin. The significance of glucosamine in beverages and foods may arise when an individual treated with warfarin ingests more than two 8-oz servings each day or ingests the enhanced beverages and other products containing forms of glucosamine such as glucosamine tablets or capsules. Theoretically, a warfarin-treated patient who drinks one 8-oz glass of orange juice in the morning and augments this with glucosamine tablets (500 mg 3 times/day) could be exposed to glucosamine 2250 mg/day. Some of the cases of an increase in the INR value discussed in this article in warfarin-treated patients appeared to be related to an increase in the glucosamine dose. At this point, we do not have sufficient clinical data to ascertain whether or not the amount of glucosamine contained in these beverages is clinically significant in patients receiving warfarin therapy. Clinical studies of glucosamine and warfarin interactions have not been performed. Patients who take warfarin should be informed that the use of glucosamine and glucosamine-containing products may lead to an increase in the INR value, and close and frequent monitoring seems prudent, at least initially.

Conclusion

The aggregate data presented in our report suggest that glucosamine use in patients stabilized with warfarin therapy may, under certain circumstances, increase the INR value and thereby increase the risk of bleeding. In light of the potential risk to these patients and a dearth of studies that elucidate the mechanism of action of glucosamine, it seems prudent to advise patients prescribed warfarin to seek alternatives to glucosamine. If the patient chooses to continue glucosamine use with warfarin, it is warranted to more closely monitor the INR.

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