Risk Factors of Drug Interaction between Warfarin and Nonsteroidal Anti-Inflammatory Drugs in Practical Setting

Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to interact with the oral anticoagulant warfarin and can cause a serious bleeding complication. In this study, we evaluated the risk factors for international normalized ratio (INR) increase, which is a surrogate marker of bleeding, after addition of an NSAID in a total of 98 patients who used warfarin. Patient age, sex, body mass index, maintenance warfarin dose, baseline INR, coadministered medications, underlying diseases, and liver and kidney functions were evaluated for possible risk factors with INR increase $\geq 15.0\%$ as the primary end-point. Of the 98 patients, 39 (39.8%) showed an INR elevation of $\geq 15.0\%$ after adding a NSAID to warfarin therapy. Multivariate analysis showed that high maintenance dose (>40 mg/week) of warfarin (P=0.001), the presence of coadministered medications (P=0.024), the use of meloxicam (P=0.025) and low baseline INR value (P=0.03) were the risk factors for INR increase in respect to NSAID-warfarin interaction. In conclusion, special caution is required when an NSAID is administered to warfarin users if patients are taking warfarin >40 mg/week and other medications interacting with warfarin.

Key Words : *Warfarin; Anti-Inflammatory Agents, Non-Steroidal; Drug Interactions*

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INTRODUCTION

Oral anticoagulation with warfarin is the established method for treatment and prophylaxis of thromboembolic diseases (1, 2). While the efficacy of warfarin on anticoagulation is well established, it can cause a potentially fatal complication, hemorrhage. Hemorrhage develops in as many as 9.6% of patients annually, including a fatal case rate of 0.6% (3).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs to control musculoskeletal pain or inflammation. In addition to their antiplatelet function, NSAIDs can affect the pharmacologic action of warfarin through their direct interaction. High protein binding and the cytochrome P450 (CYP)-dependent clearance mechanisms of NSAIDs can affect the serum levels of warfarin (4-6). Accordingly, there have been many case reports describing bleeding complications after NSAIDs were administered along with warfarin (7-13).

The level of anticoagulation with warfarin is usually monitored with international normalized ratio (INR), which is a strong predictor of future bleeding risk (2); every one-point increase in INR increases bleeding risk by 54.0% (14). Therefore, monitoring INR is essential when prescribing warfarin. In this respect, discontinuing of NSAIDs or adjusting warfarin dose should be considered if INR increases after addition of a NSAID.

In this study, we investigated the risk factors for INR increase in respect to warfarin and NSAIDs. The results of our study provide important baseline data for using NSAIDs in warfarin users.

MATERIALS AND METHODS

Study population

A total of 2,652 warfarin users were confirmed who began to take NSAIDs at the outpatient clinics of Seoul National University Hospital between January 2000 and August 2006. The patients fulfilling the following criteria were recruited for the study: 1) Maintenance warfarin dose was stabilized for at least 3 months before adding a NSAID. Stabilization

was defined as INR change within 15.0% of baseline values. Target INR value was 2.0-3.0, 2) INR values after addition of NSAIDs were available, 3) The warfarin dose did not change after adding a NSAID, and the administered NSAID dose remained constant, 4) The age of the patient was 18 yr and older. Ninety eight patients fulfilled all of the above criteria.

The Institutional Review Board of Seoul National University Hospital approved this study. All of the data were managed after the deidentification process.

Study design

This study was a retrospective case control study using medical records in a tertiary hospital. For each patient, the following data were collected from the medical records or anticoagulation service team records: age, sex, body mass index (BMI), underlying diseases, species of NSAIDs, indication and dosage of warfarin, INR values before and after the administration of the NSAIDs, baseline liver function tests (alanine aminotransferase, aspartate aminotransferase), and drugs coadministered with warfarin and NSAIDs. Liver function test abnormalities were defined as elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above the upper range of reference values (40 IU/mL). Prothrombin time (INR) was determined using the STAR analyzer, an automated nephelometric coagulation laboratory analyzer (Diagnostica Stago, Asieres, France). The intra- and inter-assay coefficients of variations (CV) of prothrombin time (PT) were 1.3% and 2.3%, respectively. Baseline INR value was defined as the last INR value before a NSAID was added. Mean duration between the point when the INR was measured and a NSAID was added was 17.4 ± 11.7 days. The first INR value measured after adding a NSAID was used for comparison with the baseline value.

Between the cases and controls of the study, the case was defined as those in whom INR was increased more than 15% after addition of a NSAID and the controls were defined as the rest of the patients. INR increase of $\geq 15\%$ was chosen because an INR increase of <15.0% can occur as a result of test variability (7). Finally, risk factors for INR increase were explored for subjects and controls.

Statistical analysis

To explore the risk factors associated with INR increase, age, sex, BMI, underlying diseases, species of NSAIDs, indications for warfarin, maintenance dose of warfarin, baseline PT (INR), baseline liver function test results, baseline renal function test results, and the presence of coadministered medications were regarded as independent variables. The presence of INR increase was regarded as a dependent variable.

Logistic regression analysis was applied to compare the cases and controls. After performing univariate analysis with each independent variable described above, multivariate anal-

ysis was done to infer the best model to explain INR increase after adding a NSAID. Independent variables which showed $P<0.100$ in univariate analysis (age, baseline INR value, maintenance warfarin dose and meloxicam) and a variable which appeared consistently in the models predicted by the progressive or deletion model (coadministered medication) were chosen as independent variables to infer the best model. All statistical analyses were done with SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study population

The study population consisted of 98 patients; the characteristics of whom are summarized in Table 1. Heart valve replacement was the most common indication for warfarin, followed by cerebral infarction, atrial fibrillation and venous thromboembolism. There were no patients who used more than one NSAID at a time. Of the 98 patients, 39 (39.8%) showed an INR elevation of $\geq 15.0\%$ after adding a NSAID to warfarin therapy.

Eighty patients used other medications than warfarin or NSAIDs; among these, 42 patients were taking comedications which might interact with warfarin (15). The comedications included acetaminophen, amiodarone, aspirin, benzb-

Table 1. Characteristics of the study population

Characteristics	INR increase after a NSAID	
	(+) n=39 (%)	(–) n=59 (%)
Patients		
Sex (female:male)	26:13	33:26
Age (mean±SD) (yr)	57.6±13.0	61.6±9.6
Body mass index (mean±SD)	22.3±3.5	23.0±3.6
Indications for warfarin (%)		
Heart valve replacement	24 (61.5)	39 (66.1)
Cerebral infarction	6 (15.4)	5 (8.5)
Atrial fibrillation	4 (10.3)	10 (16.9)
Venous thromboembolism	5 (12.8)	5 (8.5)
Maintenance dose* of warfarin (mean±SD)	33.6±10.8	28.3±10.0
NSAIDs used (%)		
Aceclofenac	14 (35.9)	18 (30.5)
Celecoxib	4 (10.3)	11 (18.6)
Meloxicam	8 (20.5)	5 (8.5)
Naproxen	5 (12.8)	7 (11.9)
Rofecoxib	1 (2.6)	7 (11.9)
Fenoprofen	3 (7.7)	4 (6.8)
Zaltoprofen	3 (7.7)	4 (6.8)
Ibuprofen	1 (2.6)	3 (5.1)
Comedications[†] (%)	20 (51.3)	22 (37.3)

*mg/week; [†]Comedications with known interaction with warfarin.
NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Risk factors for INR increase with respect to the interaction of NSAIDs and warfarin (univariate analysis)

Variables	Odds ratio (95% CI)	P value
Age	0.97 (0.93-1.01)	0.09
Sex		
Male	0.64 (0.27-1.47)	0.29
Female	1.00	–
Body mass index	0.94 (0.83-1.07)	0.35
LFT abnormalities	0.66 (0.13-3.48)	0.62
Indication for warfarin		
Atrial fibrillation	3.00 (0.57-15.77)	0.19
Venous thromboembolism	2.50 (0.46-13.65)	0.29
Heart valve replacement	1.55 (0.43-5.46)	0.51
Cerebral infarction	1.00	–
Baseline INR	0.310 (0.09-1.08)	0.07
Warfarin dose (mg/week)		
>40	13.00 (2.34-72.14)	0.003
20-40	4.76 (1.00-22.68)	0.05
<20	1.00	–
NSAIDs		
Meloxicam	11.20 (1.04-120.36)	0.046
Zaltoprofen	5.25 (0.40-68.95)	0.21
Fenoprofen	5.25 (0.40-68.95)	0.21
Naproxen	5.00 (0.46-54.51)	0.19
Aceclofenac	5.44 (0.60-49.56)	0.13
Celecoxib	2.55 (0.23-27.71)	0.44
Ibuprofen	2.33 (0.11-50.98)	0.59
Rofecoxib	1.00	–
Co-medications	1.77 (0.78-4.02)	0.17

NSAIDs, nonsteroidal anti-inflammatory drugs; LFT, liver function test (Liver function test abnormalities were defined as elevation of AST or ALT above the upper range of reference level.); INR, International Normalized Ratio; CI, confidence interval.

Table 3. Risk factors for INR increase in interaction of NSAIDs and warfarin (multivariate analysis)

Variables	Odds ratio (95% CI)	P value
Age	0.98 (0.93-1.02)	0.24
Baseline INR	0.20 (0.05-0.86)	0.03
Warfarin dose (mg/week)		
>40	19.46 (3.15-120.34)	0.001
20-40	4.87 (1.04-22.71)	0.04
<20	1.00	
Comedications	3.16 (1.17-8.54)	0.02
Meloxicam	4.88 (1.23-19.45)	0.03

INR, International Normalized Ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.

were associated with INR increase after administration of a NSAID in univariate analysis with $P<0.100$. In multivariate analysis, high maintenance dose of warfarin ($P<0.001$), the presence of coadministered medications ($P=0.02$), the use of meloxicam ($P=0.03$), and low baseline INR value ($P=0.03$) were finally fitted into the final model (Table 3).

DISCUSSION

In this study, we showed that initiating NSAIDs in warfarin users could increase INR in 39.8% of the patients. Patients who had maintenance doses of warfarin >40 mg/week took warfarin-interacting medications and used meloxicam were more susceptible to INR increase when a NSAID was added.

We chose INR increase as the clinical endpoint of the study. Measurement of INR is the standard monitoring method in warfarin users for predicting bleeding complications (1, 2). Therefore, meticulous monitoring of INR is accepted as a reasonable approach to prevent bleeding complication when NSAIDs are administered to patients taking warfarin (10, 16). Since the fatal hemorrhagic complications can occur without any preceding minor bleeding, adjustment of medication should be strongly considered if INR increases.

We defined an INR increase of more than 15.0% as significant in this study. Test variability of INR measurement is known to be 15.0% and this cut-off value was used in another study (7). Furthermore, test variability of PT in our hospital is less than 2.5%. Whether 15.0% increase is clinically significant may be controversial. However, to the best of our knowledge, there has been no clear guideline on which percent increase of INR is clinically safe or risky.

It has not been previously reported that the patients who need high maintenance doses of warfarin are more vulnerable to drug-interaction with NSAIDs. More saturation of plasma proteins or metabolic enzymes with warfarin might be the cause of more frequent drug interactions. Presence of coadministered medications other than warfarin or NSAIDs

romarone, bezafibrate, cefdinir, ceftizoxime, cilostazol, clopidogrel, deflazacort, fluconazole, hydrocortisone, indapamide, magnesium oxide, metronidazole, omeprazole, prednisolone, rosuvastatin, sertaconazole, simvastatin, SK1306X, sulfasalazine, sultamicillin, tramadol, trazodone, trimebutine, and valproic acid.

Among the 39 patients who experienced more than 15% of INR increase, 6 patients (15.4%) had to decrease the dose of warfarin after stopping it at least for 1 day and 19 patients (48.7%) had to decrease the dose of warfarin. Among the 59 patients who did not experience more than 15% INR increase, only three patients (5.1%) had to decrease the dose of warfarin. Five bleeding episodes were noted, including one intracranial hemorrhage (ibuprofen), two epistaxis (fenoprofen and aceclofenac), one hemoptysis (ibuprofen) and one muscle hematoma (fenoprofen).

Risk factors for INR increase

As summarized in Table 2, age, baseline INR value, maintenance warfarin dose and the administration of meloxicam

was another risk factor for INR increase. As described in the methods section, the study population used a wide range of comedications which were known to interact with warfarin. Therefore, the presence of coadministered medication as a risk factor is reasonably expected result. Heterogeneity of comedications among the study population may result in pleiotropic effects. However, the result of our study reflects practical clinical settings where patients have different kinds of comorbid conditions requiring different kinds of medications. Low baseline value of INR was also a risk factor for INR increase (P=0.03). This result comes from the fact that we defined INR increase as percent increase rather than absolute increase.

Among the NSAIDs tested in this study, meloxicam was found to be a risk factor for INR increase in warfarin users. Turck et al., however, reported that meloxicam lacked interaction with warfain (17). Such divergent results can be explained as follows. First, clinical settings were different; the previous report was on 13 healthy persons, while our study represents real clinical settings where distinct kinds of medications were concomitantly used. Second, response to warfarin varies depending on ethnicity (18-20). This difference is now beginning to be explained by genetic polymorphisms of the metabolic enzymes. Since induction or suppression of enzymes is one of the mechanisms of drug interaction between NSAIDs and warfarin, genetic difference of these metabolic enzymes may affect the INR level after the addition of NSAIDs (21, 22).

However, a cautious approach is needed for interpretation of the NSAID results for the following reasons. First, we tested only eight kinds of NSAIDs. The results should be interpreted in the context of the other seven NSAIDs. Second, there was no bleeding case with meloxicam in this study. Bleeding might be prevented with early detection of INR increase. If we consider bleeding cases of ibuprofen, fenoprofen and aceclofenac in our study, celecoxib or naproxen may be recommended as first line NSAIDs in warfarin users. A prospective study with a large number of patients is warranted to prove this suggestion. A careful approach is still needed when adding a NSAID in warfarin users, regardless of its class, until our suggestion is proven.

Liver function test abnormalities were not a risk factor in our patient group. These results are consistent with a previous report that the disposition of warfarin is not affected by mild or moderate hepatic impairment (23). However, since maximal levels of AST and ALT were within 5 times of the upper range, a cautious approach is needed when applying our results to the patients who have severe liver function abnormalities.

Interindividual variability in the response to warfarin is now beginning to be explained by pharmacogenetic polymorphisms. Polymorphisms of cytochrome P450 2C9 and VKORC1 genes are most commonly studied for this approach (22, 24). For NSAID-warfarin interaction, Malhi et al. reported that a patient who experienced extensive bleeding after introduction of celecoxib was a heterozygote with CYP2C9*2 and *3 alleles, which were associated with low metabolism (25). These results suggest that pharmacogenetic testing may be useful to refine the risk group for NSAID-warfarin interaction. Further studies are warranted on the role of genetic polymorphisms on the risk of NSAID-warfarin interaction.

There are several limitations in this study. First, the number of patients was limited so that all of the potential confounding variables which could affect the INR level could be evaluated simultaneously. We could enroll only 98 patients out of 2,652 candidates because INR was not measured in most of the cases after the addition of a NSAID. The low number of patients might produce a type I and II errors in the interpretation. Second, the endpoint of the study was the INR value, a surrogate marker of hemorrhage rather than bleeding although bleeding may be more clinically important endpoint. However, considering the potential seriousness of bleeding, clinicians may still have to use INR as a guideline for deciding their strategy when using warfarin. In this sense, our result will be helpful for clinicians.

In conclusion, high maintenance dose of warfarin, the presence of coadministered medications, the use of meloxicam and low baseline INR value are the risk factors for INR increase in respect to NSAID-warfarin interaction.

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