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ORIGINAL

EVALUATION OF POTENTIAL DRUG INTERACTIONS OF ORAL ANTICOAGULANTS IN ATHLETIC PATIENTS BASED ON PHARMACY INFORMATION DATABASES

Jun Xu[1#], Jinjin Yin[1#], ZhengRong Mei[1], Ying Wang[1], Shaozhi Liu[1*]

[1]The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou 510150, Guangdong, China
#: common first author
*Corresponding author: Shaozhi Liu
Email: jinjinyin1107@163.com

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ABSTRACT

AIM: The interactions between hypoglycemic drugs and other drugs were retrieved based on the pharmacy information database to evaluate the X-level/contraindication and D-level/serious potential drug interactions (pDDIs) of outpatient anticoagulant prescriptions, so as to provide a guarantee for clinically safe drug use. **METHODS:** Based on the interaction of 5 oral anticoagulants recommended in the "China Guidelines for the Prevention and Treatment of Thrombotic Diseases (2018 Edition)" retrieved from the two databases of Lexicomp and Micromedex, statistics of a hospital from January 1,2021 to 2022 During March 31st,200 outpatients with anticoagulant prescriptions for grade X/contraindication and grade D/severe pDDIs were analyzed by multivariate Logistic binary regression analysis. **RESULTS:** Among the 200 athletic patients, there were 0 pairs of grade X/taboo pDDIs,and 67 pairs of grade D/severe pDDIs, mainly due to grade D/serious potential bleeding caused by the combination of anticoagulants and non-steroidal anti-inflammatory drugs(NSAIDs) risk. Multivariate Logistic binary regression analysis found that multiple drug combination (≥5 kinds) and concomitant cardiovascular disease were risk factors for the occurrence of grade D/severe pDDIs. **CONCLUSION:** for athletic patients with multiple diseases coexisting and needing to take multiple drugs, it is necessary to pay attention to the pDDIs of anticoagulant drugs, select appropriate drugs, and avoid fatal risks such as severe bleeding. Adverse reactions after medication were closely monitored.

KEYWORDS: Anticoagulants;Drug Interactions;Databases;Case Analysis;Logistic regression

As the population ages and people's lifestyles and habits change, thrombophilia has become a major global health problem and the number one cause of death worldwide. Anticoagulant drugs are widely used worldwide and anticoagulation reduces mortality and the incidence of cardiovascular disease in athletic patients with atrial fibrillation (Kirchhof et al., 2016), and the cardiovascular benefits of anticoagulation increase the risk of bleeding, some studies have shown that anticoagulation increases the risk of gastrointestinal bleeding by a factor of two in athletic patients (Á. Lanas et al., 2015) (Radaelli et al., 2015). This risk is further increased by the combination of anticoagulants with other drugs that carry a risk of bleeding, with the risk of gastrointestinal bleeding with oral anticoagulants combined with non-selective non-steroidal anti-inflammatory drugs (ns-NSAIDs) being 2.4 times higher than when they are not combined (Masclee et al., 2014). Recent studies have shown that providing prescription streamlining electronic decision support has no significant impact on the improvement of adverse drug events (McDonald et al., 2022), while pharmacist interventions can reduce the risk of adverse reactions by 35% (Gray et al., 2018). Based on these findings, it is crucial for pharmacists to dig deeper into the safety of anticoagulant drugs when used in combination. In this study, two major international databases, Lexicomp and Micromedex, were used to search for interactions between oral anticoagulants, including the non-vitamin antagonist warfarin and new oral anticoagulants (NOVACs), and other drugs, and to investigate the X-grade/contraindicated and D-grade/severe pDDIs in 200 real-world outpatient prescriptions for anticoagulants at one hospital. The aim is to provide the best possible basis for decision making in athletic patients requiring anticoagulation therapy and to support the safe use of medication (FRICKE, 2020).

1. MATERIALS AND METHODS

1.1 Materials

1.1.1 Source of materials

A random number table method was used to extract 200 outpatient medical records of a hospital using oral anticoagulants from January 1, 2021 to March 31, 2022 with the help of the MedMu Smart Pharmacy Management software and HIS system.

1.1.2 Sources of information on anticoagulant interactions

The drug interaction information of the above anticoagulants was screened and analysed in two databases, Lexicomp and Micromedex, according to warfarin and four NOVACs (dabigatranate, apixaban, edoxaban and rivaroxaban) recommended in the Chinese Guidelines for the Prevention and Treatment of Thrombotic Diseases (2018 edition) [2], respectively, and

both databases used a five-grade scale for the severity of drug interactions, as shown in Table 1.

Table 1. Grading of drug-drug interactions by Lexicomp and Micromedex

Databases	Grading
Lexicomp	A (no known interactions) B (no intervention required) - may occur but little/no clinical evidence C (treatment monitoring) - may be clinically significant and requires monitoring D (may require a change in treatment regimen) - should be assessed to determine if the risks outweigh the benefits, requires close monitoring X (avoid combination) - risks outweigh benefits
Micromedex	Unknown No known drug interactions Weak Limited clinical effect Moderate May lead to deterioration of patient's condition and/or require alternative therapies Serious May be life-threatening and/or require medical intervention to minimise or avoid serious effects Contraindicated Contraindicated concomitant use

1.2 Methods

1.2.1 Discharge with drug interaction statistics

A random sample of 200 medical records of outpatient use of oral anticoagulants was selected and the data were statistically analysed using Excel 2007 in combination with the presence of grade X/contraindicated and grade D/serious interactions of anticoagulants retrieved from the Lexicomp and Micromedex databases. The drugs with grade X/contraindicated and grade D/serious interactions in the same class in both databases were essentially the same, and information from the same class in both databases was combined; because the included literature was not identical and individual drugs were graded differently in the different databases, they were grouped by the class of the database with the more serious interaction.

1.2.2 Multi-factor Logistic Binary Regression

Multi-factor logistic binary regression analysis was conducted to explore the factors affecting pDDIs with the help of SPSS software. $p < 0.05$ indicates that the difference is statistically significant.

2. RESULTS

2.1 Lexicomp and Micromedex database anticoagulant class X/contraindicated and class D/serious interactions statistics

The Lexicomp and Micromedex databases were consulted to collect Grade X/contraindicated and Grade D/serious interactions, which should be of particular clinical concern as they can lead to serious outcomes, as shown in Table 2.

Table 2. Lexicomp and Micromedex Class X/Contraindication and Class D/Serious Interaction Drug Statistics

Drug name	X-rated/forbidden (all)	Grade D/severe (common)
Warfarin	Hemin, mifepristone, omethicin, oxazolamide, streptokinase, tamoxifen, urokinase, vorapax, defibrinopeptide	Allopurinol, amiodarone, androgens, barbiturates, cimetidine, fenofibrate and derivatives, fluconazole, fluorouracil, ginkgo biloba, imatinib, metronidazole, miconazole, nafcillin, NSAIDs, phenytoin, rifamycin derivatives, salicylates, sodium cyclosilicate zirconate, sulfonamide antibiotics, clarithromycin, quinolones, erythromycin, azithromycin, penicillin, cefadroxil, amoxicillin, citalopram, escitalopram, mercaptopurine, cyclophosphamide, itraconazole, enoxaparin, aspirin, clopidogrel, tigretol, simvastatin, cefdinir
Dabigatranate	Anticoagulant, Hemin, rasmitane, mifepristone, omacetaxins, P-glycoprotein/ABCB1 inducer, urokinase, vorapax, itraconazole, defibrinopeptide	NSAIDs, sodium zirconium cyclosilicate, Antacids, clopidogrel, aspirin, dronedarone, tegretol, venlafaxine, desmethyl venlafaxine, citalopram, paroxetine, phenobarbital, cyclosporine, fluoxetine
Rivaroxaban	Anticoagulants, Hemin, potent CYP3A4 and P-glycoprotein inducers/inhibitors, mifepristone, omacetaxins, St. John's wort, urokinase, vopalax, defibrinopeptides	Aspirin, clopidogrel, tigretol, NSAIDs, rifampicin, P-glycoprotein inhibitors, heparins, clarithromycin, carbamazepine, erythromycin, dexamethasone, venlafaxine, phenobarbital, itraconazole
Apixaban	Anticoagulants, Hemin, Rifampicin, Carbamazepine, Phenobarbital, Phenytoin, Dexamethasone, Mifepristone, omacetaxins, St. John's Wort, Urokinase, Volapax, Defibrinopeptide	Clopidogrel, Tigretol, Aspirin, potent CYP3A4 inducers, potent CYP3A4 and P-glycoprotein inhibitors, Phenobarbital, Fluconazole, Naproxen, NSAIDs, Itraconazole
Edosaban	Anticoagulants, Hemin, rasmitane, mifepristone, omacetaxins, rifampicin, urokinase, vorapax, defibrinopeptides	Clopidogrel, Tigretol, Aspirin, Azithromycin, Clarithromycin, Erythromycin, Itraconazole, NSAIDs, P-glycoprotein/ABCB1 inducer, Verapamil, Carbamazepine, Venlafaxine

2.2 Outpatient record statistics results

The 200 cases included 142 (71%) males and 58 (29%) females, age range 19-99 years, mean age 30.400±11.997 years, 131 athletic patients with comorbid cardiovascular disease; included 43 prescriptions for warfarin, 58 prescriptions for dabigatranate, 34 prescriptions for rivaroxaban, 16 prescriptions for edoxaban, and 49 prescriptions for apixaban The number of prescriptions was 49. The number of cases involving grade X/contraindicated cases was 0 and the number of cases involving grade D/severe pDDIs was 67, of which 43 were combined with NSAIDs (except aspirin), as shown in Table 3.

Table 3. Statistical table of grade D/severe pDDIs used with anticoagulation in combination with other drugs

Name of anticoagulant	Logarithm of drug combinations and interactions	Total	Potential risks
Warfarin	Amiodarone 4; allopurinol 2; fenofibrate 1; diclofenac sodium 1; simvastatin 1	9	Combination of warfarin and simvastatin may lead to increased risk of bleeding and increased risk of rhabdomyolysis; combination with other drugs may increase risk of bleeding
Dabigatran	Aspirin 6; celecoxib 3; clopidogrel 2; magnesium aluminum carbonate 1; etoricoxib + aspirin 1	13	Antacids can reduce dabigatranate blood levels; dabigatran in combination with other drugs may increase the risk of bleeding
Rivaroxaban	Ericiclib 4; aspirin 3; clopidogrel 3; meloxicam 3; celecoxib 1; diclofenac sodium 1; etoricoxib 1	16	Increased risk of bleeding
Apixaban	Celecoxib 9; loxoprofen 7; ericiclib 6; meloxicam 2; diclofenac double-release enteric capsules 1; almagepyrine 1; lofenozide + celecoxib 1	27	Increased risk of haemorrhage
Edoxaban	Etoricoxib2	2	Increased risk of bleeding

2.3 Class D/severe pDDIs in combination of anticoagulants and NSAIDs in athletic patients with co-morbid cardiovascular disease

Of the 43 athletic patients with grade D/severe pDDIs in combination with NSAIDs (except aspirin), there were 17 athletic patients with concomitant cardiovascular disease, the others were mainly used for analgesia in athletic patients with comorbid gout, including 7 athletic patients in combination with ns-NSAIDs and 10 athletic patients in combination with selective NSAIDs (including 6 cases in combination with celecoxib), as shown in Table 4.

Table 4. pDDIs of NSAIDs combined with cardiovascular disease

Combination of drugs	Number of examples	Percentage of
Anticoagulants in combination with ns-NSAIDs	7	41.18%
Apixaban-Loxoprofen	4	23.53%
Rivaroxaban-diclofenac sodium	1	5.88%
Rivaroxaban + meloxicam	1	5.88%
Warfarin + diclofenac sodium	1	5.88%
Anticoagulants in combination with selective NSAIDs	10	58.82%
Dabigatran + celecoxib	3	17.65%
Apixaban-Celecoxib	2	11.76%
Apixaban-erixib	2	11.76%
Rivaroxaban + etoricoxib	1	5.88%
Rivaroxaban + celecoxib	1	5.88%
Dabigatran + etoricoxib	1	5.88%
Total	17	100%

Note: NSAIDs, non-steroidal anti-inflammatory drugs; ns-NSAIDs, non-selective non-steroidal anti-inflammatory drugs.

2.4 Summary of results of multi-factor logistic binary regression analysis

The overall validity of the model was analysed by using age (≥65 years), gender, whether ≥5 drugs were combined, whether PCPs were combined, whether renal insufficiency was combined and whether cardiovascular disease was combined as independent variables in the logistic regression analysis and the presence of grade D/severe pDDIs as dependent variables (P=0.000), with P<0.05 indicating that the model was valid and that multi A multifactorial logistic regression analysis identified polypharmacy (≥5 drugs) and comorbid cardiovascular disease as risk factors for the development of grade D/severe pDDIs at P < 0.05, as shown in Table 5.

Table 5. Summary of Multivariate Logistic Regression Analysis Results

Influencing factors	Regression coefficient	OR-value	P-value
Gender	0.706	2.026	0.055
Age	-0.141	0.868	0.703
Combination of ≥5 medications	1.258	3.519	0.002*
Combined use of proprietary Chinese medicines	-0.358	0.699	0.353
Combined renal insufficiency	-0.952	0.386	0.257
Combined cardiovascular disease	-1.217	0.296	0.000

*，p＜0.05

3. DISCUSSION

Oral anticoagulants include the vitamin antagonist warfarin and the newer oral anticoagulants dabigatran, rivaroxaban, apixaban and edoxaban. The risk of bleeding with anticoagulants needs to be considered in relation to the drug itself as well as the risk of co-administering the drug.

3.1 Bleeding risks of anticoagulants

A meta-analysis study published in The Lancet that included randomised controlled trials showed that warfarin significantly reduced the risk of intracranial haemorrhage but increased the risk of gastrointestinal bleeding compared with that of the four NOVACs (Ruff et al., 2014). Another study showed that apixaban, low-dose dabigatran (110mg bid), edoxaban, and edoxaban reduced the risk of major bleeding compared to warfarin. High dose dabigatran (150mg bid) resulted in a higher risk of major bleeding than apixaban, rivaroxaban and apixaban, and the risk of major bleeding was higher with rivaroxaban than edoxaban (López-López et al., 2017). The incidence of gastrointestinal bleeding was lower with apixaban, dabigatran and edoxaban compared to rivaroxaban (Lee et al., 2019). Anticoagulation therapy is used when combining the patient's condition and the bleeding risk of the drug.

3.2 The problem of combining anticoagulants with NSAIDs

The main issue identified in this survey was the co-administration of anticoagulants with NSAIDs drugs, both selective and ns-NSAIDs, with the exception of aspirin, which is cardiovascular protective, and all other NSAIDs, which are damaging to the gastric mucosa and cardiovascular.

3.2.1 Bleeding risk when anticoagulants are combined with NSAIDs

Studies have shown that concomitant administration of anticoagulants with NSAIDs, even for short-term treatment (0-3 days), increases the risk of bleeding compared with no NSAIDs, and there is no safe therapeutic window when the two classes of drugs are used together (Olsen et al., 2015). Therefore, when the NSAIDs class of drugs must be used for athletic patients on anticoagulation therapy, the selection of drugs with a lower risk of bleeding is the focus of clinical care. The degree of damage to the GI mucosa varies between the different classes of NSAIDs, with selective COX-2 inhibitors having the lowest relative risk (RR) of 2.9 for upper GI bleeding, ns-NSAIDs having the highest RR of 4.3 and aspirin RR of 3.1.

The annual incidence of serious upper gastrointestinal events such as bleeding, ulceration and even perforation associated with NSAIDs is 1.5% to 2%, four times higher than that of those not taking this class of drugs (Valkhoff, van Soest, Sturkenboom, & Kuipers, 2010). The risk of gastrointestinal bleeding was found to vary between different types of ns-NSAIDs, with ibuprofen being low, nimesulide, diclofenac and meloxicam being intermediate risk, and naproxen and indomethacin having a higher risk. The results of the study showed that the selective COX-2 inhibitor celecoxib reduced mucosal damage in the gastrointestinal tract and that the risk of bleeding with the drug was equivalent to that of ns-NSAIDs combined with PPIs [12]. This study found that the clinical dosing did not take into account the bleeding risk of athletic patients in a comprehensive manner in favour of the low-risk NSAIDs celecoxib.

3.2.2 Cardiovascular risk of NSAIDs should be measured when anticoagulants are combined with NSAIDs

There were 17 athletic patients in this study with cardiovascular disease who were also using NSAIDs, so in addition to the bleeding risk of anticoagulants the cardiovascular risk of this class of drugs should also be considered. With or without cardiovascular disease, other ns-NSAIDs and COX-2 selective NSAIDs, with the exception of aspirin, are associated with an increased risk of cardiovascular adverse events, including stroke, cardiac polyphasia, heart failure and myocardial infarction, and the first two adverse effects may occur within the first week of dosing (Food & Administration). Possible influences on the risk of adverse cardiovascular events include drug

selection, treatment course, frequency and dose (Antman et al., 2007; Vargas et al., 2020).

For clinical use, the drug with the least cardiovascular risk, i.e. naproxen, should be preferred for athletic patients with a higher risk of cardiovascular disease, but due to the insufficient availability of this drug in China, other NSAIDs with a lower cardiovascular risk, such as ibuprofen at a daily dose ≤1200 mg or celecoxib at a daily dose ≤200 mg, can be considered (A. Lanas et al., 2014) (McGettigan & Henry, 2006). Drugs with a higher cardiovascular risk including diclofenac, indomethacin, etoricoxib or rofecoxib should not be used (da Costa et al., 2016). A recent study has shown that celecoxib has a better cardiovascular safety profile compared to naproxen and ibuprofen (Obeid et al., 2022). In summary of the above literature and the recommendations of Up-to-date, celecoxib (maximum dose 200 mg/day) is recommended for those at higher risk of cardiovascular disease or in combination with cardiovascular disease without recent events, while in athletic patients with pre-existing cardiovascular disease, acetaminophen is the alternative drug of choice if possible. In this study, 17 athletic patients with concomitant cardiovascular disease were found to have ns-NSAIDs in 7 cases and COX-2 selective NSAIDs in 10 cases (celecoxib in 6 cases), suggesting that our clinic did not consider the patient's condition comprehensively to give the best dosing regimen (Armbruster, Buehler, Min, Riley, & Daly, 2014).

3.3 Class D/severe pDDIs of concern when anticoagulants are used in combination with other drugs

When administered with antacids such as magnesium carbonate, dabigatran exposure was reduced by 11%. Antacid interactions may be more significant in the 24 hours after surgery, as a 35% reduction in dabigatran exposure was observed in postoperative athletic patients within 24 hours after surgery, avoiding concomitant use with antacids for 24 hours after surgery. In other cases, dabigatran should be given 2 hours before antacids.

Allopurinol and amiodarone may potentiate the anticoagulant effect of warfarin antagonists (McInnes, Lawson, & Jick, 1981) (Lam et al., 2013) and should be monitored intensively if the combination is necessary. Fenofibrate may potentiate the anticoagulant effect of warfarin and the concomitant use of simvastatin and warfarin may lead to an increased risk of bleeding and an increased risk of rhabdomyolysis. Atorvastatin may be recommended as the first choice when lipid-lowering therapy is required in athletic patients taking warfarin, as it has no significant effect on prothrombin time during the combination of atorvastatin and warfarin.

3.4 Risk factors affecting the occurrence of grade D/severe pDDIs

In addition to analysing drug-drug interactions, this study used logistic regression to analyse objective factors that may contribute to the occurrence of serious adverse reactions. The study identified combination of drugs (≥5) and comorbid cardiovascular disease as risk factors for the occurrence of grade D/serious pDDIs. Studies have found that elderly athletic patients treated with 5-7 drugs have an approximately 1.58-fold increased risk of serious adverse reactions compared to athletic patients treated with <5 drugs [1,3,27]. Therefore, the combination of multiple drugs for combined cardiovascular disease should be screened for serious pDDIs and the optimal dosing regimen should be developed.

3.5 Summary

This study was based on a search of the pharmacy information database for anticoagulant drugs relative to serious pDDIs and an analysis of objective factors other than drugs using logistic regression, with the aim of ensuring the selection of effective and safe drugs while also considering other objective factors to reduce the occurrence of serious drug interactions and provide homogeneous management criteria for clinical drug use. The results of this study provide important insights into the work of clinical pharmacy. Drug interactions are a pressing concern for clinicians, and the results of this study may serve as a bridge between pharmacy and clinical practice, providing clinicians with optimal treatment options when simultaneous anticoagulation and analgesia are required, and are of value in clinical practice.

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