Drug Utilization Study and Adverse Drug Reaction Reporting among Patients Using Anticoagulants in a Tertiary Care Teaching Hospital

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ABSTRACT

Drug utilization (DU) is systematic regulatory approach designed to identify diversity of drugs use and to evaluate the rational use of medicines in population. Anticoagulants are drugs used to avoid thrombus extension and embolic consequences with associated risks related to their administration. Objectives: The objectives of the present study were to evaluate the drug prescription pattern of anticoagulants, observe and report drug interactions and adverse drug reactions among patients using anticoagulants. Method: Utilization of anticoagulant drugs was evaluated in 50 patients from 4 wards (dialysis, medicine, orthopedic and intensive-care unit) of a tertiary care teaching hospital in a cross-sectional, prospective study conducted for 4 months i.e. from 1st January 2018 to 30th April 2018. Results: LMWH (enoxaparin) was the maximum preferred parenteral anticoagulant prescribed to 31 % of patients as prophylaxis for deep vein thrombosis followed by heparin. 14(28%) of total population were administered combination therapy and 36 (72%) patients received only one anticoagulant drug during hospitalization. The most prescribed drug combination was enoxaparin+warfarin followed by enoxaparin+acenocoumarol. For discharge medicines, 14 patients were prescribed oral anticoagulants; 9 (64.3%) patients were prescribed with warfarin and the remaining 5 (35.7%) patients were given acenocoumarol. 28(56%) patient’s laboratory tests were evaluated for parameters like prothrombine time (PT) and international normalized ratio (INR). In the remaining 22 (44%) patients, the above tests were not performed. Sixteen drug interactions were identified, ten were pharmacodynamics and the rest six were pharmacokinetic interactions. Three adverse drug reactions were reported during the study. The need for dosage adjustment in different diagnostic situations or specific populations is very crucial. Conclusion: The therapy with these drugs needs to be cost effective and reduce the complications associated with their use.

Keywords: Anticoagulants, Drug utilization evaluation, Drug interactions.

1. INTRODUCTION

Drug utilization study is essential to evaluate prescription patterns, rational use of drugs and to develop interventions for improvement of quality of life that will enhance proper and safe administration of medicines. Absence of essential drug prescription policy, irrational drug utilization and the prevalence of self-medication, all these factors lead poor access to healthcare1. Inadequate knowledge of suitable prescription and utilization leads to increase drawbacks in evaluating the therapeutic value, cost effectiveness and adverse effects.

A venous thrombosis (VT) refers to a blood clot that starts in a vein. Deep vein thrombosis (blood thrombus in the deep veins) is associated with pain and swelling, usually in the thigh, pelvis and axillary vein and often takes place without symptoms. Thrombus formed in large veins prone to break off and trapped in pulmonary artery and ultimately impedes blood supply causing a pulmonary embolism (PE). Each year, approximately 1,000,000 Americans acquire VTE, and 100,000 deaths occur as a result. VTE is therefore estimated to produce 5–10% of all deaths among hospitalized patients and therefore, it has become an economic burden for health care. A retrospective study was conducted in India aimed to
study prevalence of VTE in high risk hospitalized patients, the incidence of VTE was 17.46 per 10,000 admissions. A homeostatic mechanism between coagulation cascade and fibrinolytic system in human body is maintained by coagulation factors. Anticoagulants reduce blood tendency for coagulation, either by direct inhibition of coagulation factors or by interfering with their synthesis. Anticoagulants do not lyse a formed clot, but they used as prophylactic and prevent recurrences. According to the National Health Service (NHS) England (2013) National VTE Prevention programme, evaluation of hospitalized patients who are at risk to develop VT should be considered. Anticoagulants are effective for venous fibrin clot and have questionable value in arterial thrombi (platelet clot). They are indicated for prevention and treatment of different kinds of cardiovascular diseases like DVT, PE, myocardial infarction (MI), unstable angina, prosthetic heart valve, major vascular operations. Heparin is used in vitro during a blood transfusion and laboratory investigations. Anticoagulants treatment monitoring is essential to avoid adverse events like bleeding by over coagulation, and thrombosis due to under coagulation. Because anticoagulants act by different modes of action and have a narrow window for therapeutic dosing, their administration requires special attention. To improve quality of the treatment and to adjust medicine intake, predictive models were introduced.

When rapid and consistent anticoagulation is required, heparin is first indicated as initial therapy, followed by oral anticoagulants as maintenance dose. Multiple drug-drug and drug-food interactions in addition to drug response variations between patients increase the difficulties for optimal treatment with vitamin K antagonists (VKA). Direct oral anticoagulants (DOAGs) like apixaban, rivaroxaban, edoxaban and dabigatran are a novel class of agents that were introduced for acute and long-term treatment of VTE.

Achieving the goal of proper usage requires special control and strict clinical and laboratory follow up. It is very important to identify and develop new standards not only to improve efficacy and safety of anticoagulants utilization, but also to minimize the complications and the cost of administration.

2. METHODS
2.1 Study Design
The study was prospective, cross-sectional and non-interventional to evaluate the prescription pattern of anticoagulants on the basis of physicians prescribing records, patient’s pro-forma and questionnaire data. Study was carried out in the HAH Centenary Hospital, Jamia Hamdard, New Delhi. Patients hospitalized in HAH Centenary Hospital using anticoagulants were counseled and their spontaneous ADRs were reported and analyzed using ADR reporting form and WHO-UMC scale. Patient’s eligibility inclusion criteria were: Patients of both sexes having more than 18 years of age who utilized anticoagulant drugs during hospitalization. The study included a total of 50 patients, utilized anticoagulant drugs either for treatment or prophylaxis along the study period of 4 months.

2.2 Data Collection
Collected demographic data of patients include age, race, sex, height, weight, medical history, underlying disease and indication(s) for anticoagulant therapy. Another data obtained from patient’s medical record like kidney and liver function markers, concomitant medications, duration of anticoagulant therapy, drug-drug/food interactions. Various laboratory investigations related to diagnosis and monitoring of anticoagulant therapy were assessed like PT, INR and aPTT. Data for the study were assessed by referring patient’s medication profile, case records, laboratory reports and study pro-forma. Patient’s adherence to the therapy on the basis of data obtained during admission using medication compliance questionnaire and spontaneous ADRs were reported and analyzed using ADR reporting form and WHO-UMC scale.

2.3 Statistical Analysis
By using Microsoft excel, data were analyzed by using descriptive statistical parameters namely, mean, standard deviation and percentage. Stockley’s drug interaction, 8th Edition used as resource to measure the severity level of drug-drug interactions. WHO-UMC interaction scale was used to observe ADRs.

3. OBSERVATION AND RESULTS
Fifty patients included in the study who received anticoagulants with different disease conditions. Out of 50 patients, 21(42%) were male patients with mean age of 59.19 years, and 29(58%) were female patients with mean age of 54 years. The study subjects were classified into four age groups; 18(36%) belonged to age group of 56 to 70 years covered majority of patients in the study, followed by 14(28%) patients in age group of 41 to 55 years. Patients in age group of 25 to 40 and 71 to 86 years were found to be same in distribution which was nine (18%) Fig. 1.
Total number of patients on single drug therapy was 36 (72%), out of which 20 (55%) patients were on Enoxaparin, followed by heparin which was prescribed to 13 (36%) patients. Two patients were prescribed with VKAs (warfarin and acenocoumarol). Only one patient was prescribed with fondaparinux. Among total patients received anticoagulant drugs, 14 (28%) were on drug combination therapy. This combination therapy included parenteral and oral drugs. The most utilized combination therapy was enoxaparin+warfarin which were prescribed to seven (50%) patients, followed by enoxaparin+acenocoumarol prescribed to 3 (21%) female patients. The least utilized combination was heparin+acenocoumarol which prescribed only to one patient Fig. 2. For discharge medicine, 14 (28%) patients were prescribed oral anticoagulants, 9 (64.3%) patients were administered warfarin and the remaining 5 (35.7%) patients were given acenocoumarol. Concurrent use of antiplatelet drugs (aspirin, clopidogrel) was also observed during the study.

![Figure 2: Combination Anticoagulant Drugs Utilization](image)

Patient’s laboratory test parameters like PT and INR were evaluated only for 28 (56%) of patients. These tests were repeated in 8 (28.5%) patients to monitor the efficacy and predict over coagulation effect of anticoagulant therapy. Most anticoagulants were prescribed in ICU Fig. 3.

![Figure 3: Anticoagulant Drugs Utilized In Different Hospital Wards](image)

Total of three adverse drug reactions were reported spontaneously. One was with heparin; one was with enoxaparin and one ADR was with warfarin. TABLE 1. WHO-UMC causality assessment scale was used to assess the causality and the result was probable ADR with heparin and enoxaparin, and possible ADR with warfarin. Few ADRs were observed, mild thrombocytopenia by heparin, hematoma by enoxaparin and nausea and abdominal pain by warfarin.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug class</th>
<th>Adverse drug reaction</th>
<th>No. of patients</th>
<th>Causality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Heparin</td>
<td>Thrombocytopenia (Platelets =87000 /ul)</td>
<td>1</td>
<td>Probable/Certain</td>
</tr>
<tr>
<td>2</td>
<td>Enoxaparin</td>
<td>Hematoma</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>3</td>
<td>Warfarin</td>
<td>Nausea, abdominal pain</td>
<td>1</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Table 1: Spontaneous Adverse Drug Reaction Reporting
The patient's medication chart was evaluated for drug interactions involving anticoagulants. A total sixteen drug interactions were identified. In eight of drug interactions, was involved in interaction with other drugs like amiodarone, clindamycin, phenytoin, diltiazem, aspirin and NSAIDs. Four interactions were observed involving heparin with drugs like aspirin, clopidogrel, piperacillin and NSAIDs. Enoxaparin with pentoxifylline and acenocoumarol with amiodarone, sulfamethoxazole, oral contraceptive (levonorgestrel) and diltiazem were the other interactions identified. Out of sixteen interactions, ten were pharmacodynamic and the rest six were pharmacokinetic interactions. The pharmacokinetic drug interaction between acenocoumarol and amiodarone is due to the mechanism that acenocoumarol acts by inhibition of vitamin K synthesis, and amiodarone acts by inhibiting the action of cytochrome P450 isozyme, this interaction results in increased anticoagulant activity. Interaction between heparin and piperacillin, results in increased anticoagulant activity with the mechanism involving being inhibition of platelet aggregation by piperacillin. One more interaction was observed in combination of warfarin with phenytoin, this combination increased prothrombin time. The mechanism of pharmacodynamic interaction was found to be a synergistic action involving drugs like acenocoumarol with clarithromycin and enoxaparin. Anticoagulant drugs were prescribed for patients having different disease conditions as shown below in Table 2.

Table 2: Reasons for Anticoagulant Drugs Administration

<table>
<thead>
<tr>
<th>Cardiovascular conditions</th>
<th>No. of cases</th>
<th>Non cardiovascular conditions</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery diseases</td>
<td>8</td>
<td>CKD</td>
<td>12</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
<td>Ischemic stroke</td>
<td>2</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
<td>AKI</td>
<td>2</td>
</tr>
<tr>
<td>IVC thrombosis</td>
<td>1</td>
<td>Knee replacement</td>
<td>2</td>
</tr>
<tr>
<td>Metric valve stenosis</td>
<td>1</td>
<td>Bone fracture</td>
<td>7</td>
</tr>
<tr>
<td>Cardiopulmonary arrest</td>
<td>1</td>
<td>Vascular lesions</td>
<td>2</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>1</td>
<td>Thrombophlebitis</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Inferior vena cava (IVC), Chronic kidney disease (CKD), Acute kidney injury (AKI).

4. DISCUSSION

The study was conducted to evaluate the prescription pattern of anticoagulant drugs among patients admitted in different wards at HAH centenary hospital, a tertiary care teaching hospital of Jamia Hamdard, associated HIMSR, New Delhi.

The present study showed that the anticoagulants prescription based on international guidelines with a little deviation. The pattern of use did not always correspond with American College of Chest Physicians (ACCP) guidelines and in some cases the prescription based on patient's requirements. Over four months of study on patients age ranged from 25 to 86 years, it was observed that there were 31% of patients followed by enoxaparin administered for 11 patients out of 400 patients were administered anticoagulants despite, there was not any drug interaction involving heparin with drugs like aspirin, clopidogrel, piperacillin and NSAIDs. Four interactions were observed involving heparin with drugs like aspirin, clopidogrel, piperacillin and NSAIDs. Enoxaparin with pentoxifylline and acenocoumarol with amiodarone, sulfamethoxazole, oral contraceptive (levonorgestrel) and diltiazem were the other interactions identified. Out of sixteen interactions, ten were pharmacodynamic and the rest six were pharmacokinetic interactions. The pharmacokinetic drug interaction between acenocoumarol and amiodarone is due to the mechanism that acenocoumarol acts by inhibition of vitamin K synthesis, and amiodarone acts by inhibiting the action of cytochrome P450 isozyme, this interaction results in increased anticoagulant activity. Interaction between heparin and piperacillin, results in increased anticoagulant activity with the mechanism involving being inhibition of platelet aggregation by piperacillin. One more interaction was observed in combination of warfarin with phenytoin, this combination increased prothrombin time. The mechanism of pharmacodynamic interaction was found to be a synergistic action involving drugs like acenocoumarol with clarithromycin and enoxaparin. Anticoagulant drugs were prescribed for patients having different disease conditions as shown below in Table 2.

From observation of our study, most of the anticoagulant drugs (36%) were administered in the intensive care unit. Warfarin was prescribed more than acenocoumarol at the time of discharge at a dose of 5mg for patients with coronary artery disease, dilated cardiomyopathy, metric valve stenosis and CKD. Acenocoumarol was used in patients with rheumatic heart disease, atrial fibrillation and vascular lesions. Heparin was found to be the only anticoagulant drug used in haemodialysis unit. The doses of heparin during haemodialysis were 5000 IU for the initial bolus and 2500 IU/hr for continuous infusion. This dose was adjusted in some cases like patients with liver diseases and blood disorders. Several recent publications have suggested that LMWHs may have potential therapeutic advantages over normal UFH. Laboratory tests like PT and INR were evaluated in 28 patients, and these tests were only repeated in 8 patients during hospitalization. The risk of gastrointestinal bleeding increases by anticoagulant drugs especially heparins, so additional occult blood stool test is recommended. None of the study patients were examined for this reason.

An interesting finding of this study, there was not any drug of DOACs prescribed; however, the new anticoagulants have obvious advantages over conventional agents. This may be due to the high cost of this class and the low patients' income.
5. CONCLUSION

Adherence to anticoagulant therapy plays a major role to improve outcomes and reduce the risk of bleeding. Medical practitioners have multiple anticoagulants administration options for the treatment and prophylaxis of VTE. Anticoagulants prescription pattern deviation from the guidelines depends on characteristics of patients, concomitant therapy and physician judgment. Appropriate dosing and monitoring of these agents help to evaluate the safety and efficacy of anticoagulant drug. Some limitations existed in our study; among them were small sample size, Single center and Language barrier during patients counseling.

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CONFLICT OF INTEREST

No conflict of interest

REFERENCES


