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*Original Article*

# Enoxaparin Utilization Evaluation: An Observational Prospective Study in Medical Inpatients

Fanak Fahimi[a,b], Shadi Baniasadi[a*], Neda Behzadnia[c], Fatemeh Varahram[a] and Leila Ghazi Tabatabaie[a]

[a]*Pharmaceutical Care Unit, TB and Lung Diseases Research Center, NRITLD, Masih Daneshvari Hospital, Shahid Beheshti University, M.C., Tehran, Iran.* [b]*Clinical Pharmacy Department, School of Pharmacy, Shahid Beheshti University, M.C., Tehran, Iran.* [c]*Cardiology Department, Masih Daneshvari Hospital, Shahid Beheshti University, M.C., Tehran, Iran.*

**Abstract**

Drug utilization evaluation (DUE) is an effective program to identify variability in drug use and to support interventions that will improve patient outcomes. The appropriate use of enoxaparin, a low molecular weight heparin (LMWH), which is widely used as curative or preventive treatment of thromboembolic disorders was assessed in the study.

A prospective DUE was carried out at Masih Daneshvari teaching hospital. Criteria for the appropriate use of enoxaparin was used to evaluate prescription and administration patterns in this hospital.

Enoxaparin utilization of 147 inpatients was reviewed. A total of 944 variables (70.92%) in the regimen, among all subjects, were rated as appropriate and 382 (28.70%) were rated as inappropriate for the conditions diagnosed.

The results of this study showed that inappropriate dosing, administration and prescribing of enoxaparin is rather common in masih hospital. Educational programs and implementation of protocols may be needed in the teaching hospitals to control prescribing patterns.

**Keywords:** Enoxaparin; Drug utilization evaluation; Prescription pattern; Appropriate drug use.

## Introduction

Drug utilization evaluation (DUE) is a program to identify variability in drug use and to support interventions that will improve patient outcomes. The effectiveness of DUE programs has yet to be established (1-3).

Drug use indicators are intended to measure specific aspects of health providers and drug use in a hospital or health center. Indicators will provide information to health care managers concerning drug use, prescribing habits, and important views of patient care. They reflect the status of an important characteristic of the given health care service (4).

The primary goal of the present study was to investigate the best target for DUE in different wards of a respiratory teaching hospital.

A preliminary investigation was performed to identify a drug that: 1: had been the highest-cost/highest-volume item, 2: had been prescribed in the hospitals for at least three years, 3: had not been subjected to any prior DUE or intervention to change physicians prescribing behaviors, and 4: would be a clinically relevant target for

* Corresponding author:
E-mail: baniasadi@nritld.ac.ir

a DUE. Enoxaparin was the only drug to meet these criteria in our setting.

We could only find one review, which mainly evaluated the therapeutic doses of enoxaparin in a British hospital. The audit showed that dose calculation based on the patient weight could be cost saving (5).

Low molecular weight heparin (LMWH) offers many advantages to both the patient and the clinician in the treatment of deep vein thrombosis (DVT), over the traditional acute care setting treatment of patients with unfractionated heparin (UFH) (6). Enoxaparin is a LMWH, which is widely used as curative or preventive treatment of thromboembolic disorders (7).

This study was conducted to determine whether prescriptions and administration of the selected drug in the hospital complied with the official recommendations. In addition, the data recorded on misuse or inappropriate therapy were made available to the physicians to evaluate and optimize its administration.

## Experimental

This study was conducted in Masih Daneshvari hospital, which is a university-based hospital specialized in lung diseases.

In a prospective DUE, observed patterns of drug prescription, and administration together with an evaluation of their appropriateness, were entered into a pre-designed form aiming both at improving prescribing patterns and preventing inappropriate prescribing in the future.

Criteria for the appropriate prescription and administration of enoxaparin (Table 1) were made available to us by a selected scientific committee consisting of the authors, pharmacy administrative representative, and a clinical pharmacy specialist from a different university, who evaluated the appropriateness of enoxaparin use at the hospital. Criteria pertaining to indication for use, combination therapy, dosage, cautions, monitoring parameters, contraindications and administration were used. The stated criteria were approved by the Drug and Therapeutic Committee (DTC) of the hospital.

This study assessed the prevalence of any inappropriate utilization of enoxaparin.

Pearson correlation was used to assess correlations, where applicable.

## Results

From July 2005 to October 2005 a total of 147 inpatients receiving enoxaparin (Clexane®, Aventis™) were identified. The patients were 86 males and 61 females and their mean age was 57.13±16.17 years (range: 21-86).

Indications for enoxaparin use included venous thromboembolism (VTE) prevention in patients with surgery: 4.8%, VTE prevention in patients without surgery: 54.4%, DVT with or without Pulmonary Emboli (PE): 19.7%, unstable angina: 19.7%, and others: 1.4%.

The percentages of patients whose management met each of the criteria have been summarized in Table 2.

Variables considered in this study included: indication, dose, duration of therapy, administration technique, monitoring parameters, concurrent warfarin indication and duration, and special population consideration. A total of 944 (70.92%) variables in the regimen, among all subjects, were rated as appropriate and 382 (28.70%) were rated as inappropriate for the conditions diagnosed. Of the 382 inappropriate uses, 79 (53.74%) doses administered were found to be inappropriate and 111 (75.51%) inappropriate, in terms of the duration of treatment or prophylaxis. Baseline activated partial thromboplastin time (aPTT) and complete blood count (CBC) were not requested for 12 (8%) and 5 (3.40%) patients, respectively. Activated partial thromboplastin time and CBC were ordered for 91 (62%) and 112 (76.19) patients, respectively, during the administration of enoxaparin. The stool occult blood test was not requested for any of the subjects. Eight patients had creatinine clearance (ClCr) < 30 ml/min and appropriate dosage adjustment was performed for 4 patients consistent with the approved criteria. Forty one patients had an indication for concurrent warfarin therapy. Warfarin was not prescribed for 6 patients, despite indication, but was prescribed for one patient with no indication. Six patients (18.18%) out of 33, with appropriate warfarin indication, did not receive concurrent warfarin therapy for a sufficient period of time. Five patients were obese and yet enoxaparin was

**Table 1.** Criteria for the appropriate prescription and administration of enoxaparin.

| |
|---|
| **Indications** |
| - Prophylaxis of deep vein thrombosis or pulmonary emboli in patients undergoing surgery.<br>a High risk patients: 40 mg/d, for 7-10 days, starting 12 hours before surgery unless spinal/epidural anesthesia is to be performed.<br>b Moderate risk patients: 20 mg/d, for 7-10 days, starting 2 hours before surgery unless spinal/epidural anesthesia is to be performed.<br>c Total hip replacement therapy (not applicable in our hospital).<br>- Prophylaxis of deep vein thrombosis or pulmonary emboli in medical patients: 40 mg/d, for 6-14 days.<br>- Treatment of deep vein thrombosis: 1 mg/kg BD or 1.5 mg/kg/d for an average of 10 days. Warfarin therapy initiation within 72 Enoxaparin administration should be continued for a minimum of 5 days , until a therapeutic anticoagulant effect has been achieved (target International Normalization Ratio (INR)) (14).<br>- Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in patients with chronic renal failure (not applicable in our hospital).<br>- Treatment of unstable angina or non-Q-wave MI, concomitantly with ASA: 1 mg/kg BD, for 2-8 days (9). |
| **Contraindications** |
| Uncontrolled active bleeding, severe hypertension, hemorrhagic stroke, allergy or hypersensitivity to heparin, pork products or to the LMWH, a history of thrombocytopenia with the specific LMWH, or a positive in vitro platelet aggregation test in the presence of the specific LMWH (22). |
| **Risk factor for bleeding** |
| Coagulopathy, prior history of bleeding with heparin, arterial hypertension, thrombocytopenia, retinopathy, surgery, history of hemorrhagic stroke, recent stroke, male<57 kg, female<45 kg, and CrCl<30 ml/min (14) . |
| **Cautions** |
| Patients with a history of heparin-induced thrombocytopenia (HIT), or undergoing spinal or epidural anesthesia, septic endocarditis, major blood clotting disorders, blood dyscrasias, active gastric or duodenal ulceration, injuries to or surgery involving the CNS, eyes or ears, diabetic or hemorrhagic retinopathy, or severe hepatic or renal insufficiency, and pregnant patients with mechanical valves (14). |
| **Monitoring** |
| Routine PTT and CBC counts are recommended.<br>Periodic complete blood counts (CBCs), including platelet counts and stool occult blood tests are also recommended during the course of treatment.<br>Enoxaparin does not consistently modify activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin clotting time (TT); therefore, treatment cannot be monitored with these tests (12, 14).<br>Children, pregnant women, and obese patients (BMI >30) should start with heparin (14). Those with severe renal insufficiency should switch to IV heparin (15-17) or their dose should be adjusted,in terms of the following criteria:<br>- Not more than 20 mg/d for prophylactic dosage ranges.<br>- Not more than 1 mg/kg/d for treatment dosage ranges (14). |
| **Nursing considerations** |
| The SC injection should be alternated between the left and right anterolateral or posterolateral abdominal wall. Patients should be supine and the whole length of the needle should be introduced vertically into a skin fold held between the thumb and index finger (15). The skin fold should not be released until the injection is complete. Do not rub the injection site after administration (9). |

ordered for all of them. One patient switched to heparin later on. Per investigator oberservation, once for every patient, appropriate needle insertion technique was not performed in 33 (22.4%) cases. Massage at the injection-site was applied in 8 (5.4%) cases (Table 2).

Bleeding occurred in 8 cases (5.44%), 2 with epistaxis, 3 with hemoptisis, one with melena and 2 with an unknown origin. None of the patients with bleeding had renal insufficiency (ClCr < 30 ml/min).

Four (50%) patients with bleeding had other risk factors for bleeding. Among them 2 had a history of prior bleeding, one thrombocytopenia and one female weighing less than 45 kg.

Concurrent anti-platelet therapy was performed in 5.1% of the patients.

Using the pearson correlation analysis,a correlation between anti-platelet therapy and bleeding during enoxaparin administration was found. In addition, we found no significant ($p>0.05$) correlation between the use of

**Table 2.** A summary of the appropriateness* of enoxaparin use.

| Variable | Inappropriate number (%) | Appropriate number (%) | Unknown number (%) |
|---|---|---|---|
| Indication | 0 (0) | 147 (100) | 0 (0) |
| Dose | 79 (53.74) | 64 (43.53) | 4 (2.72) |
| Duration | 111 (75.51) | 35 (23.80) | 1(0.68) |
| Introduces needle vertically to the skin | 33 (22.4) | 114 (77.6) | 0 (0) |
| Injection-site massage | 8 (5.4) | 139 (94.6) | 0 (0) |
| Baseline PTT monitoring | 12 (8) | 135 (92) | 0 (0) |
| PTT monitoring during therapy | 91(62) | 56 (38) | 0 (0) |
| Baseline platelet monitoring | 5 (3.40) | 142 (96.59) | 0 (0) |
| Platelet monitoring during therapy | 35 (23.81) | 112 (76.19) | 0 (0) |
| Stool occult blood tests during therapy | 147 (100) | 0 (0) | 0 (0) |
| Switching to IV heparin or dose adjustment if CrCr < 30 ml/min† | 4 (50) | 4 (50) | 0 (0) |
| Concurrent warfarin therapy‡ | 7 (17.07)§ | 33 (80.49) | 1(2.44) |
| Duration of concurrent warfarin therapy‡ | 6 (18.18) | 26 (78.79) | 1(1.03) |
| Switching to IV heparin if body mass index (BMI) >38¶ | 4 (80) | 1(20) | 0 (0) |

* Based on the criteria approved by DTC.
† A total of eight patients had ClCr<30 ml/min. The percentage is calculated accordingly.
‡ A total of 41 patients had indication for concurrent warfarin therapy.
§ Warfarin was not ordered for 6 patients, despite indication.
¶ A total of 5 patients were obese.

angiotensin converting enzyme inhibitors (ACEIs) and potassium level changes in patients on enoxaparin.

## Discussion

Based on the results of this study, inappropriate dosing, administration and prescribing of enoxaparin were not uncommon in our hospital.

Only patients who received enoxaparin were evaluated for the appropriateness of the indication. We did not assess patients with enoxaparin indication, who had not received the drug, and they were excluded from this investigation.

A one-year study in elderly patients, on potentially inappropriate prescribing, showed a total of 28.7% inappropriate doses (8). There were missed opportunities (53.74%) for optimal enoxaparin dosing, which would integrate weight-based dosing and/or dose adjustments in our findings. Jetha found that 16% of the enoxaparin doses required adjustments (5). Duration of therapy was another issue, in which this study looked upon. The length of enoxaparin administration was not in accordance with the defined criteria for 75.51% of the cases.

With regards to the criteria approved in our setting and manufacturer's recommendation, the whole length of the needle should be introduced vertically into a skin fold, in order to inject enoxaparin. Enoxaparin was administered with an improper injection angle, in 22.4% of the cases.

Based on the information provided by the manufacturer of enoxaparin, the frequency of injection-site hematomas with this drug is 10% or greater (9). Most minor bleedings with enoxaparin in the TIMI 11B study were attributed to ecchymosis at the subcutaneous injection site or to a hematoma at the site of a sheath inserted for cardiac catheterization (10). Injection site massage can aggravate these reactions.

PTT test was requested for 91 cases (62%) while platelet monitoring (although recommended) was not performed for 35 cases (23.81%) on enoxaparin.

The need for frequent laboratory tests, i.e.

activated partial thromboplastin time (aPTT), the time spent on these tests, as well as the staff involved from patient's bedside to laboratory, could result in extra costs and potential complications in patients. According to a pharmacoeconomic evaluation of enoxaparin, the itemized cost for one PTT monitoring per day added 45$ to the expenses (11).

Close monitoring of platelet counts are recommended during enoxaparin administration (12). Although rare, cases of thrombocytopenia have been reported. Manufacturer recommends discontinuation of therapy if platelets count drops below 100,000/mm.

Stool occult blood tests are recommended during therapy because of the risk of bleeding with heparins (10). None of the study patients were examined for this reason.

Clearance of the anti-factor Xa effect of LMWH is significantly related to CrCl.

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully, using anti-factor Xa levels (12). Monitoring of anti-factor Xa levels was not in need of conduction in our hospital.

Eight patients had ClCr<30 ml/min and dose was adjusted for 4 of them. Exposure to enoxaparin increased with the degree of renal impairment. Thus a dosage adjustment is necessary for patients with severe renal impairment (clcr<30 ml/min). Although dosage adjustment is an accepted option in patients with severe renal impairment (14), alternative drug treatments with unfractionated heparin is recommended, based on the evidence based guidelines (15-17).

There is no consensus for adjusting/correcting the weight-based dosage of LMWH for patients who are morbidly obese. Monitoring of antifactor Xa levels in this special population may be justified (15). Though clinically significant differences between the groups in peak anti-Xa levels or in time to elimination of the drug was not reported (18). One obese patient out of five was switched to heparin, later in the course of therapy.

None of the patients with bleeding had renal insufficiency, in contrary to the result of the reported by Khazan (19), who found bleeding ($p$=0.063) to be most frequent when renal impairment was present. A study on 208 patients receiving enoxaparin revealed risk factors with an increased risk for minor or major bleeding. These were increased age, coadministration of nonsteroidal anti-inflammatory drugs or antiplatelet drug therapy, and the number of enoxaparin doses administered (20).

In another study, potassium levels were found to increase on the third day of treatment with enoxaparin. (21). However, we did not see any increase in potassium levels.

Based on the pre-study calculations, it was found that enoxaparin accounted for the highest cost and volume in our hospital.

Some limitations existed in our study, which should be addressed. Among them was the fact that although this study was designed as a prospective evaluation, there still may had been data which were extracted by chart review, and hence poor documentation of relevant data could have influenced the validity of the results.

This type of review can alert the physicians of the need for changes in medications' prescribing patterns and monitoring, or the need for dosage adjustments in different indications, special populations, etc. This is mainly useful when a specific prescription is compared with some form of best practice or guideline. The key physician(s) must then be alerted so that educational programs and protocols can be implemented (17).

In conclusion, holding educational programs and implementation of protocols, especially for more expensive and frequently used medications, may be needed in the teaching hospitals to control prescribing patterns.

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