Product Management and Efficacy Evaluation of an Anti-Coagulant Enoxaparin (Clexane) in Pakistan

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Abstract

Objective: Enoxaparin (Clexane) is a low molecular weight heparin with a molecular weight of around 4500D. It is a blood thinner used to treat pulmonary embolism, Deep vein thrombosis, unstable angina, non-ST elevated myocardial infarction and ST-segment elevation myocardial infarction.

This project is designed to evaluate the most widely used Low molecular weight heparin (LMWH), enoxaparin in patients with Acute Coronary Syndrome (ACS) based on prescriptions evaluation.

Methods: Prescriptions were collected from different health institutes and were evaluated on the basis of Market Share, MIP data-competitors, MIP data- indication, and on MIP data-specialty. The study included both male and female patients of age ranging between 50-70 years. The results reflect the prescription patterns of enoxaparin (Clexane) by evaluating 73 prescriptions from major cardiovascular hospitals in Pakistan between February 2008 and October 2008.

Results: The prescription pattern showed that physicians in Pakistan have a tendency of prescribing enoxaparin with other drugs. The results also showed that patients were prescribed multiple anti-coagulants concomitantly, including enoxaparin and aspirin.

Conclusion: Overall, the analysis of anti-coagulants has indicated that enoxaparin is the drug of choice for the treatment of ACS.

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Introduction

Product management is an effective way of identifying the variations in drug use and provides an understanding of how well a product is performing compared to its competitors on the market. Good management techniques increase the effectiveness of an organization by increasing the customer base and therefore increase profitability. It involves several key areas such as; great product planning skills, product marketing, program management and project management.

There are several processes that occur between product development and the final marketed product which is targeted to satisfy a specific consumer group. Identifying the consumer and catering to their needs is a vital step in successful product management. However, other areas such as motivation of sales team, training of supervisors, product positioning statement, budget of marketing cost, researching targeted customers, and following the trends of market requirements are equally important.

In terms of the product enoxaparin (Clexane), it is a low molecular weight heparin (LMWH) which has a molecular weight of approximately 4500D. It is an anti-coagulant, blood thinner, used to prevent and treat pulmonary embolism (PE), Deep vein thrombosis (DVT), unstable angina, Non-ST elevated myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI)/MI. In comparison to natural heparin, enoxaparin is characterized by a clear increase in the ratio between anti-Xa and anti IIa which is always greater than 4.[1] The Clinical indications for enoxaparin may vary from one country to another.

Enoxaparin works by binding with anti-thrombin III, thus protamine sulfate is used to neutralize its anti-coagulant effects. Enoxaparin is available in the following strengths; 20mg, 40mg, 60mg, and 80mg strengths, and in pre-filled syringes. It can be administered just once a day (24-hours subcutaneously (S/C) or intravenously (I/V)) but should not be injected intramuscularly (I/M). Enoxaparin has been found to be more cost-effective over alternatice products.

This study is designed to evaluate the efficacy of the most widely used Low molecular weight heparin (LMWH, enoxaparin) locally available in markets of Pakistan in patients with Acute Coronary Syndrome (ACS). The study was also designed to assess the administration pattern of anticoagulants in the presence of multiple dosage regimens based on the evaluation of clinical prescriptions, and also to assess the clinical impact.

Methods

Prescriptions were collected from the major cardiovascular hospitals of Karachi, Pakistan, these were; National Institute of Cardiovascular Disease (NICVD), Tabba Heart Institute (THI) and Karachi Institute of Heart Disease (KIHD).

The project was intended to collect prescriptions from different cardiac health centers for patients mainly suffering from hypertension, acute coronary syndrome (ACS), ischemic

syndrome and angina pectoris. Around 73 prescriptions were collected during the period of February 2008 to October 2008. The study group included patients with age ranging between 50-70 years. The prescriptions were divided into seven patient groups based on their age (Table 1).

The prescriptions indicated that four to six drugs were prescribed per patient concomitantly including multiple anti-coagulants such as low molecular weight heparin (enoxaparin) and aspirin.

Prescriptions were collected from different institutes. The patients included both males and females and their age ranged between 50 to 70 years. The study was supported by evaluating the market shares using the Medical Index of Pakistan (MIP) data-competitors (%) and MIP data-indication wise and with respect to the MIP data-specialty wise.

Results

The prescription pattern shown (Table 1) indicated that physicians in Karachi, Pakistan tend to prescribe enoxaparin in combination with different drugs. Different clinical trials have shown that enoxaparin significantly reduced the cardiac ischemic events, and provided maximum effects with maximum benefits.

Table 1: Age-wise Grouping of Patients in ACS

S. No	Age range of patients	Concomitant medication Generic + (brand)	Dose	LMWH	Dose and route of LMWH
1	65-70years	Clopidogral (*Lowplat*) Aspirin (*Disprin*) Ranitidine (*Zantac*) Morphine (as *anaesthesia*)	75mg 4 tab stat 300mg OD 2ml I/V 2cc I/V	Clexane (enoxaparin)	80mg S/C BD 3days
2	65-70years	Isosorbide dinitrate (*Isoket*) Tenormin (*Atenolol*) Aspirin (*Ascard*) Clopidogral (*lowplat*)	10ml/kit infusion 100mg OD 75mg OD 75mg OD	Clexane	80mg S/C BD 3days
3	50-55years	Isosorbide dinitrate (*Isoket*) Aspirin (*Disprin*) Tenormin (*Atenolol*) Clopidogral (*Lowplat*) Glycerine trinitrate (*Angised*)	5-8d/min 300mg ½ OD 100mg OD 75mg BD 0.5mg s/l SOS	Clexane	80mg S/C BD 4days
4	55-60years	Aspirin (*Ascard*) Clopidogral (*lowplat*) Simvastatin (*Recol*) Glycerine trinitrate (*Angised*)	75mg OD 75mg OD 20mg BD 0.5mg S/L SOS	Clexane	80mg S/C BD 3days
5	50-55years	Glycerine trinitrate (*Angised*) Aspirin (*Ascard*) Lisinopril (*Zestril*) Clopidogral (*Lowplat*)	0.5mg S/L SOS 75mg OD 5mg OD 75mg OD	Clexane	60mg S/C BD 3days
6	60-65years	Isosorbide dinitrate (*Isoket*) Aspirin (*Disprin*) Tenormin Clopidogral (*Lowplat*)	5-8d/min 300mg ½ OD 50mg OD 75mg 4tab stat	Clexane	80mg S/C BD 3days
7	Approx 50 years	Glycerine trinitrate (*Angised*) Captopril (*Capoten*) Frusemide (*Lasoride*) Clopidogral (*Lowplat*)	0.5mg S/L SOS 25mg ½ TDS 40mg OD 75mg OD	Clexane	80mg S/C BD 3days

LMWH: Low Molecular Weight Heparin;

Fragmin (Dalterparin), another low molecular weight heparin was used in two different studies; Fragmin in Unstable Coronary Artery disease (FRISC I) and Fragmin Instability in Coronary artery disease (FRISC II), the studies were used to compare the efficacy and safety of fragmin with unfractioned heparin (UFH), but the results showed that fragmin administration was more effective than UFH only in acute phase while in prolonged treatment, it did not provide any additional clinical benefits.

The Thrombolysis in Myocardial Infarction (TIMI IIB) trial was conducted to compare the efficacy and safety of enoxaparin (Clexane) in the management of Unstable Angina (UA)/Non- Q Wave Myocardial Infarction (NQWMI) over Unfractionated heparin (UFH) and results showed a significant reduction in composite end points of death, MI, and urgent revascularization. The results of Thrombolysis in Myocardial Infarction (TIMI IIB) and Efficacy and Safety of Enoxaparine in Non–Q-Wave Coronary Events (ESSENCE), meta-analysis (TESSMA) were sustained even at one year follow up.[5,6]

The ACUTE II study indicated that the combination of Tirofiban (an GpIIb/IIIa inhibitor) with enoxaparin was safer and more effective compared to the combination of tirofiban with UFH at reducing bleeding complications, urgent revascularization and re-hospitalization in patients of UA.[7]

In the NICE-3 study, where enoxaparin was used in combination with GpIIb/IIIa inhibitors (glycoprotein IIb/IIIa inhibitors; antiplatelet agent) in patients who underwent percutaneous coronary intervention (PCI), the results showed a significant reduction in death, MI and urgent revascularization. The study also concluded that PCI can be more safely managed with enoxaparin compared to UFH.[8]

The analysis of 6 controlled trials (ESSENCE, A to Z trial, SYNERGY, TIMI 11B, ACUTE II and INTERACT) of 22,000 patients across the spectrum of ACS, enoxaparin was found to be more effective and safer than UFH at preventing the combined end points of death and myocardial infarction (MI). There was also no significant increase in major bleeding. These findings, support the role of enoxaparin as an effective anti-coagulant in patients with Non-ST elevated acute coronary syndrome (NSTE ACS).[9, 10]

Discussion

Enoxaparin provided more effective ischemic reduction over UFH in patients of unstable angina and NSTEMI. This study observed that once enoxaparin has been prescribed, there was no need for routine coagulation monitoring, plus enoxaparin provided more predictable and consistent anti-coagulation effects, this is because enoxaparin does not bind to plasma protein, endothelial cells, or platelets, therefore providing more than 92% bioavailability.[11]

Enoxaparin significantly reduced death, MI, recurrent angina and the need for urgent revascularization i.e. percutaneous translumenal coronary angioplasty (PTCA) and the results were maintained even at one year follow up of the ESSENCE study. Moreover, enoxaparin can be safely used in patients who undergo for PCI.[12-14]

Some data reported that low molecular weight heparin is more effective in comparison to unfractionated heparin, as it is easy to administer, does not required any monitoring as in unfractionated heparin. The safety and efficacy of low molecular weight heparin is batter than that of unfractionated heparin in coronary heart disease patients.[15]

A Study has also confirmed the benefits of Lovenox (enoxaparin sodium injection) in the Management of High-Risk Non-ST-Elevation ACS Patients.[16]

The Continuous prescription of enoxaparin showed that the product provided the desired therapeutic effects within the limited timeframe expected by doctors and patients, but also because it is a life saving product which is used in emergencies to treat ACS.[11, 15, 21] Enoxaparin is convenient to use, does not require monitoring, and due to its great efficacy and safety profile, and the fact that it is very cost effective; it was concluded that the enoxaparin is the first choice anticoagulant in Pakistan. On the whole, these results were consistent with data provided in previous investigations.[5-7, 12]

The Market share for enoxaparin was derived from IMS (International Medical statistics), collected from the product's sales data directly from the distributors according to demand. Heparin accounts for an estimated 102.4 million of the Total market, from which enoxaparin is the market leader constituting to 75.85% of the market share (Fig. 1).

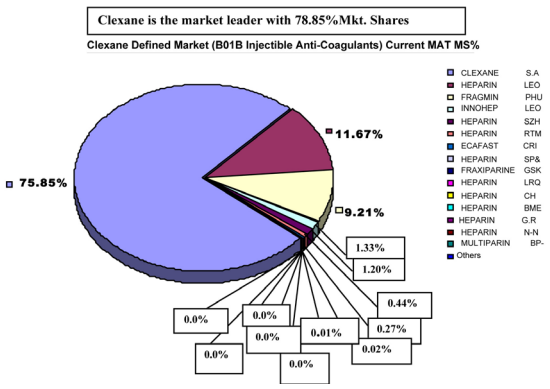

Figure1: International Market Share of Clexane

The MIP (Medical Index of Pakistan) demonstrates the number of total prescriptions for heparin collected across Pakistan. Fig. 2 shows the MIP data of competitors (%) and enoxaparin accounted for 33% of the shares because the figures also included

the prescriptions for DVT (Deep vein thrombosis). However, Fig. 3 MIP data- indication wise shows that enoxaparin has a major prescription share of 70,000 prescriptions but 52% of which are prescription for cardiovascular conditions out of the total heparin Rx of 215,000.

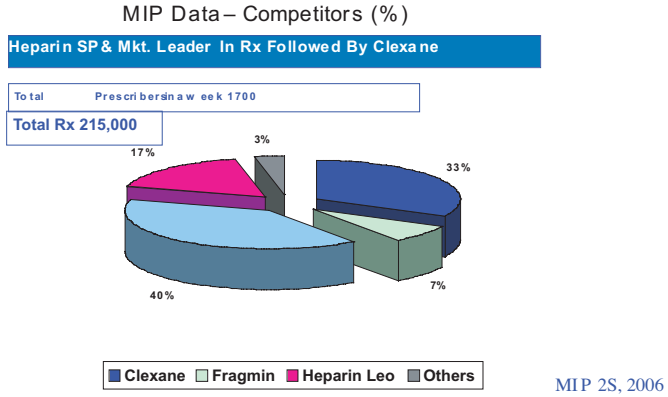

Figure 2: Presentation of Total Prescription of Heparin according to MIP.

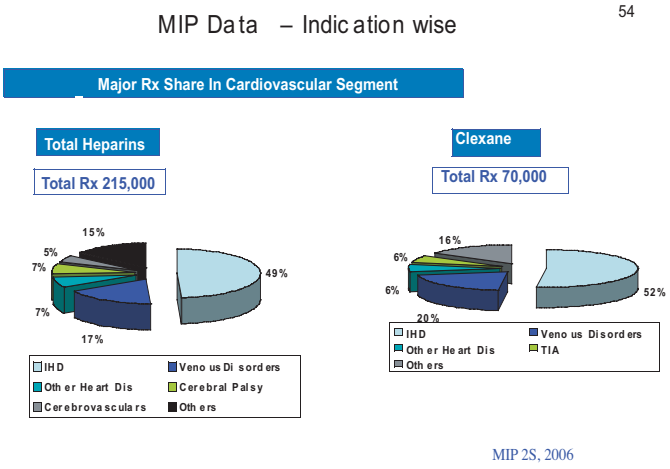

Figure 3: MIP Data on the Basis of Patient's Indication

On the other hand, the Specialty wise MIP data for heparin and enoxaparin (Fig. 4), clearly shows that Cardiologists and Physicians prefer to prescribe enoxaparin compared to other brands because it has been proven to be more effective with maximum benefits within a minimum timeframe, but also showed that there was a strong relationship between the Product Manager for enoxaparin and Key Opinion Leaders (KOLs) which has resulted from the way that the enoxaparin brand is marketed and managed through successful product management techniques.

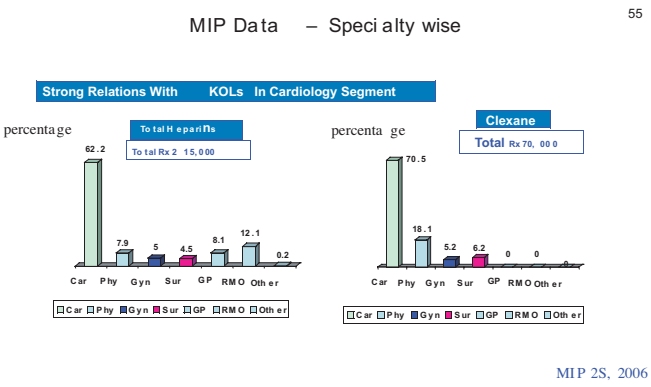

Figure 4: MIP data on the basis of Consultancy

Conclusion

Overall, the analysis of anti-coagulants has indicated that enoxaparin is the drug of choice particularly for the treatment of ACS. The conclusion was based on the national guidelines for Unstable Angina Pectoris and Non-ST Segment Elevation Myocardial Infarction established by the Pakistan Cardiac Society and Scientific Council on Atherosclerosis and Thrombosis held in 2003. This estimation has been based on the Market Index of Pakistan.

The data from literature supports the role of enoxaparin as an effective anti-coagulant in patients with Non-ST elevated acute coronary syndrome (NSTE ACS), having large duration of action that reduces the dose and it is also a cost effective products. The main significance of this study was to provide pharmacoeconomical review of clexane use focusing on the local market of Pakistan.

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