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Original

Analysis and Characterization of the Pharmacotherapy of Low Molecular Weight Heparins Prescribed in Hospitalized Patients at the Hospital Clinica Biblica (Costa Rica) from March to August 2010

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Abstract

Aim: To analyze the prescription of low molecular weight heparins in hospitalized patients at the Clinica Biblica Hospital (private hospital in Costa Rica) based on the guidelines established by the American College of Chest Physicians (ACCP;2008).

Material and methods: This study included 1651 hospitalized patients in the period from March to August 2010 who were treated with low molecular weight heparins, 250 patients were analyzed and randomly selected. A compilation of documents and information required for each patient for the analysis was made.

Results: A total of 43% of the hospitalized patients used low molecular weight heparins (707 patients). In 91% of cases low molecular weight heparins were used with a prophylactic purpose. 2% of patients did not need to use prophylactic heparin therapy. In 90% of cases the dose was correct. 18% of cases required dose adjustments. In 80% of the patients had clinically relevant drug interactions, 4% of patients had some form of bleeding, where 2% of cases this effect was linked to the use of low molecular weight heparins. In 9% of cases in which LMWH were used as treatment were addressed in accordance with established guidelines.

Conclusion: In the Hospital Clinica Biblica low molecular weight heparins were used according to the recommendations established by the guidelines of the ACCP despite the non-existence at the time of a hospital protocol. A pharmacotherapeutic analysis by the clinical pharmacist can provide important information to the medical doctor in order to take corrective and / or preventive actions associated with the correct use of medications. Make correct risk stratification and individualization of treatment facilitates proper implementation of drug therapy with low molecular weight heparins in this hospital where there is a high proportion of patients that may develop thromboembolic events.

Keywords: Low molecular weight heparins, Drug utilization study, Deep vein thrombosis, thromboprophylaxis, side effects, bleeding.

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Abbreviations: ACCP, American College of Chest Physicians; LMWH, low molecular weight heparin; CBH, Clínica Bíblica Hospital; ISHM, Integrated System for Hospital Management; PTE, pulmonary thromboembolism; VTE, venous thromboembolism; DVT, deep venous thrombosis.

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Low molecular weight heparin (LMWH) is composed of active fractions of heparin that are produced by different fractionation and chemical or enzymatic depolimerization processes and that possess less adverse effects but the same anticoagulant power as their conventional counterparts. The use of LMWH as an antithrombotic agent provides important advantages in comparison with the unfractioned heparin mainly because of its higher bioavailability and half-life, a more predictable anticoagulant response and a less stringent need for monitoring by laboratory tests.[1-6]

The type of thrombogenic substrate determines the use of LMWH for antithrombotic treatment. The main conditions where LMWH is preferred are: pulmonary thromboembolism

(PTE), stroke, myocardial infarction, transient ischemic seizures and treatment or prophylaxis for deep venous thrombosis (DVT).[4,7]

Routine assays have demonstrated that pharmacologic prophylaxis for DVT must be the treatment of choice in most patients hospitalized for more than one or two days, after risk stratification (main indication for LMWH)[7]. A single daily dose of LMWH is effective and safe, and it halves the risk of DVT without and increase on hemorrhagic complications.[7]

LMWH is widely used in the aforementioned indications, and, therefore, it is important to be able both to evaluate the efficacy or safety of the prescription and the way it is issued and its compliance with the accepted guideline (ACCP 2008 in our case). The latter variables are quantifiable by means of medication use evaluation studies.[8]

Medication use evaluation studies can provide plenty of information and multiple useful answers for the improvement of the management of drugs in a hospital, in order to accomplish a more rational use of them, to reduce the cost of treatments or to improve the way health conditions are treated.[8-12]

The American College of Chest Physicians (ACCP) guidelines have been developed in order to assure the rational and correct use of anticoagulant therapy (including LMWH among others), by means of therapeutic proposals based on the best available scientific evidence.[8]

The aim of this study was to characterize and analyze the indications for LMWH prescribed to patients hospitalized in the Clínica Bíblica Hospital (CBH) and to provide an analysis of the anticoagulant pharmacotherapy (with LMWH) that those patients received in order to validate the pertinence, efficacy and safety of these drugs, their use in view of the international guidelines (ACCP 2008) and their safety through time.

Materials and Methods

This research was a retrospective, observational medication use evaluation study. The study was carried out on hospitalized patients at CBH from March to August 2010.

All patients over 18 that received LMWH were included except those who were not hospitalized for at least 24 h. The sample size was determined by a simple random probabilistic system. Daniel Wayne's 1998 [9,10] formula for a known population with 95% confidence, 5% precision and an expected proportion of 50%, which maximizes the sample size, was employed, and random selection was achieved by the use of Microsoft Excel, Microsoft Office 2010.

All documents and necessary information for the study (clinical data for every patient, discharge report, nursing administration sheets, hospital's admission databases, epicrisis, clinical laboratory tests, medical notes, pharmacologic profile, among others) were gathered by means of the medical records and two in-house softwares at CBH: the Integrated System for Hospital Management (ISHM) and RECETARIO.

The information was centralized using a data collection sheet on which the most relevant aspects of each patient were recorded.

A comparison between the data obtained in the study and those reported in the literature[11] was carried out. A multivariate analysis including patient, disease and prescribed medicine-related factors was performed. The requirements for dose adjustment for each patient were evaluated by means of their clinical laboratory test data and the use of the creatinin clearance (Cockroft-Gault) adjusted at 72 kg.[12,13]

The need for thrombo-prophylaxis was analyzed individually using an adaptation of the system used by the ACCP and stratifying patients in one of the four VTE risk levels according to the type of adequate surgical procedure, age and the presence of other additional risk factors the patient may have had.

The dosing for each indication was evaluated according to the literature review and what has been published by the ACCP. In order to determine clinically significant interactions we used two softwares: Micromedex ® 1.0 (Healthcare Series) by Thompson Reuters and Lexi-ComInteract ®, analyzing the validity and significance of the information they generated. For the processing of the data we used statistical analysis tools and programs such as Excel Microsoft Office 2010 and SPSS V18 (Statistical Program for the Social Sciences).

The access to and review of the medical records was authorized by the institution's Medical Direction and local Pharmacotherapy Committee (a Scientific Ethics Committee was not available at the time).

Consequently, the researchers vow to ethically and morally safeguard the anonymity of the data collected.

Results

A total 1,651 patients were hospitalized during the study period. Of these, 707 were given any kind of LMWH, which represents 43% of the total hospitalized patients. A sample of 250 patients was selected from this group.

Fifty-eight percent of the selected patients were women and 43% were men. The mean age of the patients was 62 ± 15 years.

LMWH types that were used were enoxaparin (87% of the cases), bemiparin (8% of the cases), and fondaparinux (5% of the cases). Sixty-five different initial diagnoses were found, the most relevant of which are presented in Table 1.

In this hospital, the main condition where LMWH was used was DVT prophylaxis (91% of the cases). In a small

Table 1. Most relevant initial diagnoses in patients included to analyze the pharmacotherapy with LMWH. CBH, March-August 2010.

Initial diagnosis	(%)
Chronic cerebrospinal venous insufficiency (CCSVI)	14
Extirpation surgery	9
Trauma	6
Bronchopneumonia	5
Hip surgery	5
Obesity	4
DVT	5
Cardiac insufficiency	3
Knee surgery	3

group of patients (remaining 9%) LMWH was used for medical treatment of PTE, DVT, acute coronary syndrome and/or stroke. Patients who were treated under these conditions were given LMWH following the established guidelines, with correct doses and in combination with other necessary anticoagulant or antiplatelet agents.

In order to be able to stratify the patients to assess the need for thromboprophylaxis as recommended by the ACCP, an analysis of individual risk factors was carried out and the most relevant are presented in Table 2.

According to the risk stratification, 52.4% of the population had a medium risk of suffering a thromboembolic event. Forty-two point seven percent had a high risk and 3.9% a low risk. Only 0.9% of the cases did not present any risk (Figure 1). Ninety-eight percent of the population included in the study and that received LMWH did require it. The LMWH treatment was changed in 4% of the patients without a clinically valid justification.

Table 2. Frequency of risk factors among the group of patients selected for the evaluation of LMWH pharmacotherapy. CBH, March-August 2010.

Risk factor	Frequency	(%)
Age more than 45 years	197	79
BED for more than 4 days	69	28
Arterial Hypertension	137	55
Cardiopathy	76	30
Diabetes mellitus	36	14
Dyslipidemia	61	24
Obstructive pulmonary disease	12	5
Neoplasia	40	16
Obesity > 20%	51	20
Varicose veins	7	3
Arthritis	8	3
Use of oral contraceptives	4	2
Use of hormonal replacement therapy	7	3
Previous stroke	19	8
Previous myocardial infarction	12	5
Nephrotic syndrome	13	5
Cardiac failure	20	8
History of lower limb fracture	47	19

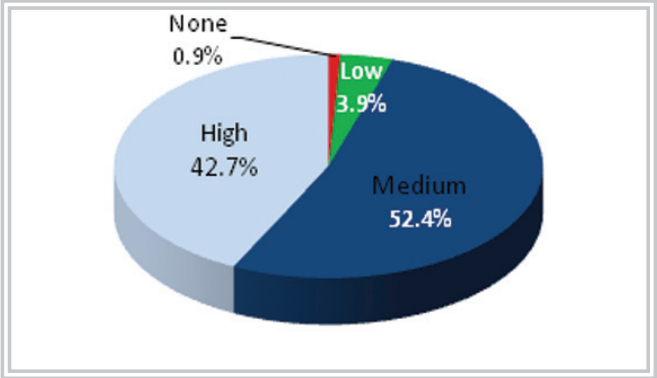

Figure 1. Thromboembolic risk distribution of the patients included for analysis of the pharmacotherapy with LMWH at CBH. Over 50% of the patients had medium risk and only 3.9% had low risk.

The right LMWH dose according to the guidelines was used in 90% of the patients, but in 19% of the cases the dose had to be adjusted later on. The dose was modified in 86% of the cases that required this, but in 22% the adjustment was not correct. Eighty-one percent of the patients received the medication for the correct length of time.

Regarding multiple drug administration, we found that 60% of the patients were receiving 6 or more concomitant drugs alongside the LMWH (Table 3). A clinically relevant pharmacologic interaction as determined by the Micromedex ® and Lexi-Com ® softwares was detected in 80% of the patients (40% showed one interaction, 29% 2 interactions, 8% three interactions, 3% four interactions, and a sole case representing 1% showed 5 interactions).

Only 9% of the cases reported secondary effects, and the most frequent were bleeding and abdominal pain (Figure 2). Among those ones that reported bleeding (4%), half of the cases included the concomitant use of a drug with antithrombotic or antiplatelet properties. Among the remaining 2%, this secondary effect was associated to the use of LMWH.

Ninety-six percent of the analyzed cases did not show any thromboembolic complication during the hospitalization period. There was only one case of DVT and another one with PTE (less than 1% for both), but in both cases the patients were receiving the correct dose of the drug.

Regarding the laboratory tests performed on the selected patients, we found that 32% of the patients had prothrombin time (PT), 29% had activated thromboplastin time (aTPT), 33% had an INR, 9% had D dimer, and 79% had serum creatinin.

Table 3. Proportion of selected patients having concomitant medications along with LMWH. CBH, March-August 2010.

Number of concomitant drugs	%
0-5	40
6-10	37.2
> 10	22.8

Discussion

The results from this study show that an important percentage of hospitalized patients (43%) received some type of LMWH, a proportion which is higher than that reported for a hospital in Madrid (36%), but similar to another report from the ENDORSE study (39%).[14,15] A higher proportion of female patients receiving this medication was also identified by this study and others.[14-18]

Among the anticoagulant drugs analyzed in this study, enoxaparin was much more commonly used (86%), a fact also reported by Villar in 2004.[17] Even though the ACCP guidelines do not specify any LMWH type, we believe that the preference towards this particular one is mainly due the higher amount indications and of clinical trial data available for it, something that may generate more confidence among prescribing clinicians.[3,4,6,7,19-23]

As was expected according to previous reviews, in this hospital the main condition for which LMWH was used was DVT prophylaxis (91%). Most patients had either a medium or a high risk of developing thromboembolic complications, making a high proportion of potential LMWH users. In this study, in 98% of the cases where LMWH were used as prophylaxis the treatment was correctly selected, which means that, even though there is not a current institutional protocol on this, clinicians at CBH perform an adequate risk stratification.

Data from this study showed that the dosing of the patients was correct in 90% of the cases. Although the ACCP guidelines do not specify on doses, they do state that: "for each of the antithrombotic agents it is recommended that medics follow the dosing instructions issued by the manufacturer".[11] A caveat to this is that the use of enoxaparin at 20 mg was considered as correct in the relevant cases. However, the sole

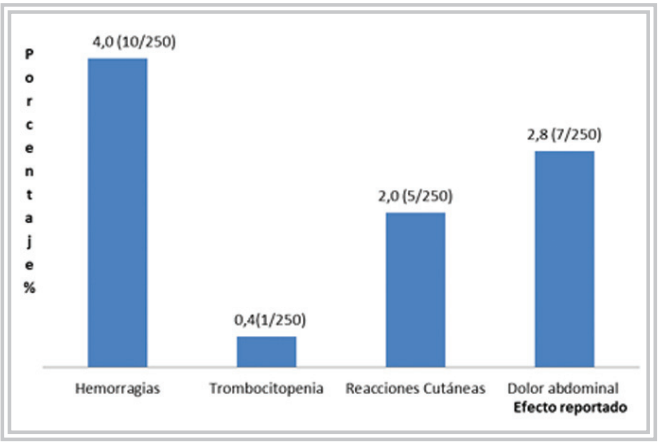

Figure 2. Proportion of secondary effects found among the patients selected for the analysis of LMWH pharmacotherapy. CBH, March-August 2010. The most frequent secondary effect was bleeding. However, this was present in only 4% of the cases.

study comparing 2 doses of enoxaparin (Medenox®) showed that the 20 mg dose was insufficient to prevent episodes of VTE when compared to a 40 mg dose, which suggests that the thrombo-prophylaxis with this LMWH in in-patients should be performed with higher doses.[19,24]

Either because of the presence of a secondary effect or because of a deterioration of renal function, especially among elderly patients, some cases required an adjustment of the dosage. The guidelines recommend making adjustments when the creatinin clearance is lower than 30 mL/min, and this is something that must be considered and corrected where needed. Nineteen percent of the patients required a dose adjustment, and this was performed in 86% of the cases but 22% of these adjustments were incorrect possibly because of lack of clinical data. The Department of Pharmacy must be obliged to help the clinician with the necessary dosage adjustments by means of constant pharmacotherapeutic surveillance.

Eighty percent of the patients presented some clinically relevant pharmacologic interaction during their treatment. Adverse effects because of the concomitant use of different kinds of drugs were not observed, but this must not imply that one should not be aware of the possibility of these complications and of the clinical relevance of the data generated by these softwares and the correct use of this information prior to any intervention. It must be stressed that the information should be available before and not after a problem arises, in order to help the clinician decide following a correct risk-benefit analysis.

International guidelines underscore the fact that different types of LMWH should not be exchanged[25,26] and that each one must be tested individually in clinical trials for each indication.[26]Despite this, 4% of the patients had a change in the LMWH they were receiving, and in none of these cases was there a clinical or pharmacologic justification. This could be due to a personal preference from the prescribing clinician since in most cases this happened in parallel to a change of the treating clinician.

The safety of LMWH in the studied population was satisfactory (9% of the patients had secondary effects) as has been reported by others.[7,14,19,27,28] Only 4 patients (2%) had bleeding which could only be associated to LMWH and this is in agreement with what has been reported in the literature.[14-18]

Four percent of the patients that received LMWH prophylaxis suffered thromboembolic events, which is slightly lower to the results obtained in a study that evaluated VTE prevention.[19]

Even though one of the advantages of LMWH is that it does not require periodic laboratory test monitoring, the ACCP guidelines and much of the literature recommend that this control must be undertaken in cases where there is a concomitant use of other drugs that can increase the risk of bleeding.

In some cases, LMWH were used in (prophylactic) indications not yet approved by any international guideline. None of the studies on the safety and efficacy of the treatments for chronic cerebrospinal venous insufficiency, such as those where the patients undergo the insertion of stents or the dilation of jugular veins with balloons, has provided detailed data on this respect.[29,30] Both procedures imply risks associated with elastic retraction, rupture of the vein, and development of blood clots. This does not mean that the prophylactic treatments from these surgeries will not be considered in the future, but that there is a lack of research that demonstrates that LMWH is safe and effective in cases such as palliative care of multiple sclerosis.[31]

Additionally, we recommend that the hospital improve the controls for the correct recording of the clinically relevant data such as weight and height of each patient and to encourage the inclusion of all necessary information on the medical records among staff, in order for it to be available for future studies. Also, once established at the institution, it should be advisable to keep an up-to-date protocol for the therapeutic management of LMWH (as defined by the ACCP) and to allow the Department of Pharmacy to fully engage in the process of pharmacologic monitoring.

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