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Contribution of Heparinemia in the Monitoring of Anticoagulant Treatments about 10 Cases and Review of the Literature

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Abstract

(HNF) and low molecular weight heparins, used for biological monitoring of heparin-like anticoagulant therapy. This work aims to show the quality of heparin management thanks to the biological monitoring by anti-Xa activity in 10 cases. The average age of our cases was 58.9 years with a frequency peak between 55 and 57 years (40%) and a clear male predominance. The most common clinical entity was the recurrence of deep vein thrombosis of the lower limbs, which was present in 40% of cases with inpatient management in the cardiology department. Our patients had all undergone heparin treatment according to the indications in force, but because of its better benefit / risk contribution the LMWH administered rate exceeded that of the UFH (70% against only 30% UFH). The activated partial thromboplastin time (APTT) value is either insufficiently prolonged for 25% of patients with UFH, or inconclusive during LMWH treatment because TCA is the almost exclusive reflection of anti-IIa activity (antithrombin).). It is for this reason that biological monitoring by measurement of anti-Xa activity is necessary and justified to ensure effective anticoagulation in targeted therapeutic areas without failing to signal the occurrence of induced thrombocytopenia. by heparin or overdose.

Although the measurement of the anti-Xa activity is little requested and difficult to achieve in our context, it remains the reference method for monitoring patients on heparin-type anticoagulants.

Keywords: Anti-Xa activity/TCA/LMWH/NFH

Introduction

Unfractionated heparins (UFH) or low molecular weight heparins (LMWH) dominated the scene as the most widely prescribed therapeutic class of anticoagulants in various indications, both preventive and curative for several decades. Heparins require for some patient populations, rigorous biological monitoring. Indeed, these products have one or more constraints: a narrow therapeutic margin, a random bioavailability, an inter-individual variability, a risk of iatrogenic effects (haemorrhage, heparin-induced thrombocytopenia). This situation leads the biologist to practice his art in close relationship with the clinician to understand the mechanisms of action, adjust the dosage of the drug and avoid iatrogenic accidents. Moreover, the effect of heparin can not be evaluated by measuring its concentration, as is the case for other molecules, but by measuring its potential to inhibit factor Xa and factor IIa. . This is why the different heparins are characterized by their ratio of anti-Xa / anti-IIa activity. However, in clinical practice, the

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handling of heparins is solely in terms of anti-Xa activity. In addition, in the quest for ever better efficacy, one of the elements making it possible to limit the risk of occurrence of an iatrogenic accident, while maintaining an anti-thrombotic benefit, is to optimize the balance of the level of anticoagulation by biological monitoring by measuring the anti-Xa activity of heparins.

Patients and methods

Our work is a retrospective study on a series of 10 cases of measurement of anti-Xa activity collected in the Hematology laboratory of HMIMV Rabat, over a period of one year stretching from January 2008 to January 2009 In this study we included patients under heparin treatment; either LMWH type Enoxaparin Lovenox® or HNF type heparin calcium
Calciparine®, the indication of determination of the anti-Xa activity for the patients of our series was: The control of the treatment of the thromboembolic disease in preventive as in curative, the monitoring of the preventive heparin treatment at the patients hem dialysis, the verification efficacy of curative heparin treatment for a patient followed for multiple myeloma complicated with vena cava thrombosis and control of heparin therapy for patients with myocardial infarction. The determination of heparin is done by chronometric dosing on STA line devices. We excluded patients from this study for difficulties evaluating heparin treatment or for side effects. Our study was done at the Military Hospital of Avicenna Marrakech from the analysis of the data of patients who were hospitalized in intensive care, cardiology, nephrology, clinical hematology at the Military Hospital. Instruction Mohammed V of Rabat, using a heparinic card for patients who had a myocardial infarction.
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Results

During the study period, 10 cases of anti-Xa activity measurements were performed at the HMIMV hematology laboratory in Rabat. The age of our patients ranged between 52 and 68 years with an average age of 58.9 years, the sex ratio was 2.3 in favor of men. In our series we found that 40% of patients were hospitalized in cardiology, 30% in medical intensive care, 20% in nephrology and 10% in clinical hematology (Chart 1). Virtually 40% of patients had recurrent deep venous thrombosis of the lower limbs (lower limb thrombophlebitis), 20% had chronic renal failure at the hemodialysis stage, 20% had myocardial infarction, 10% had a pulmonary embolism, 10% had superior vena cava thrombosis complicating multiple myeloma (Figure 2)

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pulmonary embolism, 10% had superior vena cava thrombosis complicating multiple myeloma. The history of deep thrombosis of the lower limb and uncontrolled hypertension represented the most reported antecedents with a frequency of 29% each. For therapeutic data: Three patients had received heparin preventive therapy, including one with UFH and two with LMWH (Table I). Seven patients underwent curative treatment with heparins, two with UFH and five with LMWH (Table II).

Table I:Distribution of patients according to the dose of heparin administered during preventive treatment

Type of heparin	HNF Calciparine® (UI x 2/j)	LMW Lovenox® (UI anti Xa x 2 / jr)
Dose	5000	3600 4200
Effective	1	1 1

With respect to the biological monitoring of heparin treatment, we found that TCA was more than twice the value of the control for three patients under UFH
however, in LMWH patients there was no significant change in the value of TCA. On the other hand, the value of the anti-Xa activity varied according to the type of haprine and the dose administered.

Table II: Distribution of patients according to the administered dose of heparin during a curative treatment.

Type of heparin	HNF Calciparine® (intravenouscontinuous or discontinuous)	LMW Lovenox® (UI anti Xa x 2 / jr)
Dose	400 à 800 UI/Kg/24h	100 UI anti Xa/Kg/12h
Effective	2	5

Discussion

This work reports the experience of the Hematology Laboratory of the Mohammed V Medical Military Hospital in Rabat, one of the few laboratories in Morocco that determines anti-Xa activity (heparinemia). It presents a global overview on the surveillance of patients undergoing

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heparin treatment with a view to obtaining effective anticoagulation, particularly in the referential therapeutic zones. It provides information on the epidemiological characteristics of patients included in our study as well as on the circumstances of diagnosis. The age group most concerned by the use of heparin-type anticoagulants in our study was between 55 and 57 years old (40% of cases), which is consistent with the results of the study done at the University Hospital of Fez [1]. However, according to the ANSM (National Agency for the Safety of Medicines and Health Products), people aged between 75 and 84 years are the most likely to use heparin as an anticoagulant since the incidence of thromboembolic diseases increases exponentially with age [2]. The use of the prescription of heparins in our study population as well as that of the University Hospital [1] for ages much lower than those in the literature, is explained by the failure of the primary prevention system against thromboembolism . To begin a curative or preventive heparin treatment whose indication is valid, all our patients were hospitalized with an accurate diagnosis [3, 4, 5, 6, 7]. HTA and deep vein thrombosis of the lower limbs were the main antecedents reported by our patients. Hypercoagulability and stasis were risk factors found in our study as well as in the P. Pottier et al [4] study. As in the literature, the results of our study show that the use of LMWH far exceeds the UFH, with 70% of patients on LMWH enoxaparin type sold under the name of Love ox against

Only 30% under HNF in the form of calciparin marketed under the name Calciparine®, given its better benefit / risk contribution [11]. Thus, therapeutic protocols have been adapted according to the data of the literature for the cases of our study [9]. As stipulated in the recommendations of good practice (RBP) on prevention and treatment of venous thromboembolism in medicine written in December 2009 by a group of experts under the auspices of the French Agency for Sanitary Safety of Products Health (AFSSAPS), we performed a platelet count before starting heparin treatment in all cases in our series, which proved normal with physiological values between 150,000 and 450,000 / mm3. During the period of hospitalization no patient had clinical manifestations suggestive of heparin-induced thrombocytopenia; moreover, the cases in our study were classified in the area at risk of incidence of HIT low less than 1% [2]. We opted for the biological monitoring of heparin-treated patients in our series with TCA and heparinemia, as well as literature data [2, 9, 10, 11, 12].

To obtain reliable results, it was necessary to proceed by respecting the different phases, analytical and post analytical pre-analysis. This last phase focuses on the interpretation and validation of results. The results of the TCA and the anti-Xa activity vary according to the type of heparin LMWH or UFH and according to the preventive or curative therapeutic protocol. For TCA the control time is set for each lot of reagent. A deviation of more than 6 seconds from the control, or a TCA ratio of the patient / TCA of the control> 1.2, are considered pathological. The therapeutic index sought during treatment with UFH corresponds to a TCA equal to 2 to 3 times the value of the control.

According to the results of our study, we found that UFH causes a prolongation of TCA explained by the inhibition of thrombin (IIa) whereas the greater inhibition of Xa by LMWHs makes that the TCA is little or not elongated [2, 10, 9]. On the other hand, the lengthening of the TCA during a treatment, preventive or curative, by the UFH does not bring about significant variations in the values obtained. The measurement of anti-Xa activity is a specific test that

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measures the rate of inhibition of factor Xa, expressed in anti-Xa IU / ml. It is used for monitoring treatments with heparins, UFH or LMWH and remains the only valid method and especially the most sensitive for the measurement of their biological activity. The target values of the anti-Xa activity are given in the tables (III, IV, V, VI). The literature recommends monitoring by measurement of anti-Xa activity during prophylactic or curative treatment with UFH when TCA is not contributory, in resuscitation patients and in case of marked inflammatory syndrome [13, 14, 15]. As concluded in our series
30% of cases were admitted to medical resuscitation, while other patients had an intricate inflammatory mechanism, whether in the genesis of their pathologies or as a result, which justified the demand for measurement of anti-inflammatory activity. -Xa in both cases [2, 10, 11]. For the biological monitoring of LMWH during prophylaxis, we measured the anti-Xa activity for the two patients who were in renal insufficiency which is validated by the literature data [2, 6, 7, 9]. In case of prolonged treatment beyond 5 to 8 days or chronic renal insufficiency (keratinize clearance below 60ml / min) or in subjects with extreme weights or during the occurrence of bleeding or the thrombus extension, these are all indications recommended by the literature for the measurement of anti-Xa activity in patients undergoing treatment with LMWH [2, 9, 11]. We found that the measurement of anti-Xa activity adjusts the dosages to ensure effective anticoagulation to avoid overdose (sufficient dose) while controlling the risk of bleeding (overdose) and to guide the therapeutic decision is by stopping the preventive treatment or consider relaying with ant vitamins K if a curative treatment is maintained, this after obtaining the values in the therapeutic areas of reference.

Conclusion

The demand for measurement of the anti-Xa activity is, for a very particular population (subjects in renal insufficiency, or with extreme weights or subject aged over 60), or in case of prolongation of the heparin treatment of more than 8 days, or a non-contributory TCA, for the purpose of monitoring the heparin treatment instituted to treat thromboembolic disease.
The prescription of heparin-like anticoagulants and its monitoring requires close collaboration between the clinician and the biologist. The patient should be extremely vigilant when interpreting the results of heparinemia and TCA to ensure therapeutic efficacy while preventing the risk of occurrence of HIT or heparin overdose. And in order to optimize the management quality of heparin treatment, we need to get the attention of biological laboratories and clinicians to improve the accessibility and feasibility of heparinemia when the indication arises.

References

1-M. Benjelloun, W. Bono, Z. Souirti, Z. Souirti, H. Akoudad, H. Akoudad, F. Belahsen , F. Belahsen, O. Messouak O. Messouak, M. Khatouf , M. Khatouf, M. Harrandou, M. Harrandou, N. Madani , N. Madani4, N. Kanjae, N. Kanjae. Epidémiologie de la maladie thromboembolique veineuse au CHU Hassan II de Fès : Etude de 94 cas.Presse Med 1996;25(36):1777-80.

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2-Philippe Cavalié, Nathalie Grené, Evelyne Falip, Bénédicte Hay, Stéphanie Hueber, Sara Miranda, Aurore Tricotel, Marie-Laure Veyries. Etat des lieux et surveillance.ANSM - Juillet 2012

3-Joseph Emmerich. Maladie thromboembolique veineuse : traitement et étiologie. Revue Sang Thrombose Vaisseaux Volume11,numéro 5,Mai1999, page 337-342.

3-*5T*C. Demange*5T,1T 1T5T*I. DI Sandro*5T,1T 1T5T*F. Coince*5T,1T 1T5T*S. Philippe*5T*. Observation des pratiques de prescription des héparines de bas poids moléculaire. en médecine Journal de Pharmacie clinique. Volume 18, numéro 2, Juin 1999,page156-160.

4-Cambou J.P.*P P* ; Genes N.*P P* ; Vaur L.*P P* ; Renault M.*P P* ; ETienne S.*P P* ; Ferrieres. ; Danchin N. Epidémiologie de l'infarctus du myocarde en France: Spécificités régionales. Revue d'Archives des maladies du coeur et vaisseaux 1997,vol.90,n*P*o*P*11,pp.1511-1519(26 ref.)

5-Jean-Baptiste Rey, Vincent Launay-Vacher. Utilisation des héparines de bas poids moléculaire (HBPM) chez le patient insuffisant rénal en milieu hospitalier. J Pharm Clin 2011;30(2):61-74.

6-O. Sy, N. Rolin, M. Monchi. Anticoagulation en épuration extrarénale. Reanimation (2009)18,376-384.

7-Bernard Boneu, Françoise Nguyen, Jean-Pierre Cambus. Difficultés et pièges de la surveillance des traitements par l'héparine. Sang Thrombose Vaisseaux 2003;15,n°3:131-4.

8-Sébastien Faure. Héparines de bas poids moléculaire. Fiche pharmacothérapeutique pratique. Actualités pharmaceutiques.n°523.février2013.

9-Sébastien Faure. Héparines non fractionnées. Fiche pharmacothérapeutique pratique. Actualités pharmaceutiques, n°522, janvier 2013.

10-Bernard Boneu, Françoise Nguyen, Jean-Pierre Cambus. Difficultés et pièges de la surveillance des traitements par l'héparine. Sang Thrombose Vaisseaux 2003;15,n°3:131-4.

11-P. Niclot, Anticoagulants:héparine non fractionnée, héparine de bas poids moléculaire, anticoagulants oraux. Protocole d'utilisation en urgence. Fiche technique n°2.

12-Activité anti-Xa. Précis de Biopathologie Analyses Médicales Spécialisée.Biomnis 2012.

13-Boutières-Albanèse B. Mesure de l'héparinémie par activité anti-Xa. Encyclo Med Biol, Elsévier,Paris, 2003.

14-*5T*C. Flaujac*5T,1T 1T 5T*C. Guinet*5T,1T 1T 5T*M. M. Samama*5T*. Dosage de l'activité anti-Xa des héparines de bas poids moléculaire (HBPM) du fondaparinux et des nouveaux anticoagulants.Biotribune magazine, trimestriel aout 2011, Volume38, Issue 1, pp 22-25.

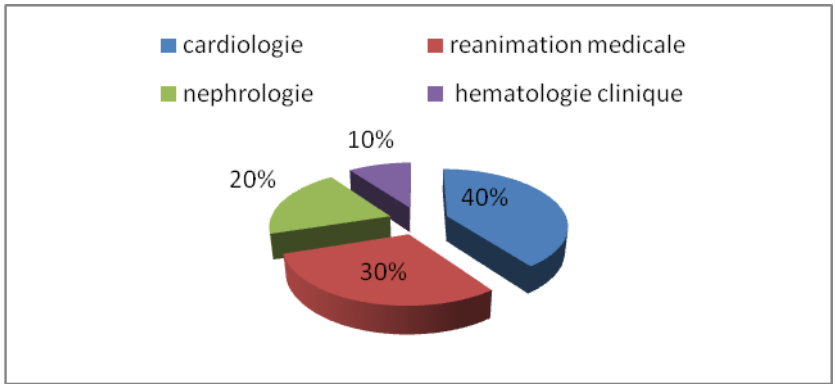

figure 1: Distribution of patients by unit of hospitalization

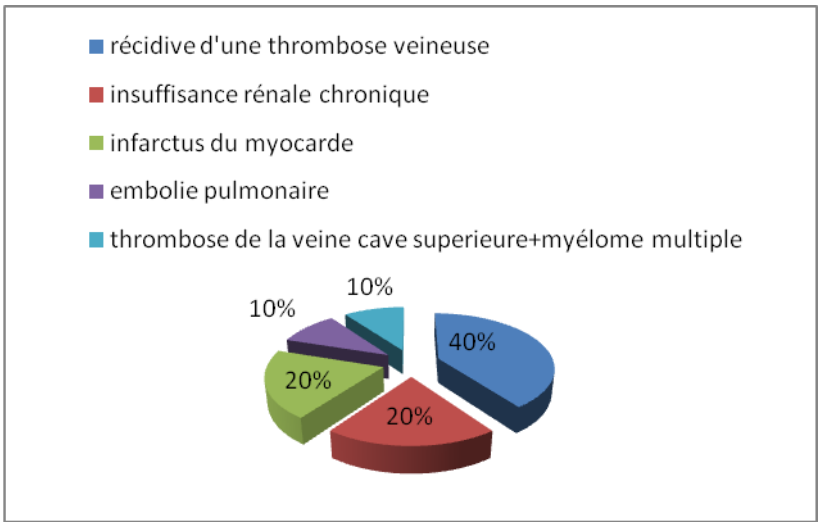

figure 2: Distribution of patients by reason of hospitalization