EARLY EXPERIMENTS IN THROMBO-PROPHYLAXIS WITH NEW ORAL ANTICOAGULANTS - RIVAROXABAN

TIBERIU TRUSCA[1], OLIVERA LUPESCU[2], MIHAIL NAGEA[1], CRISTINA PATRU[1], GHEORGHE ION POPESCU[2]

[1]Orthopedics and Trauma Clinic, Emergency Hospital, Bucharest
[2]University of Medicine and Pharmacy" Carol Davila", Orthopedics and Trauma Clinic, Emergency Hospital, Bucharest

Abstract

Rivaroxaban is a recently introduced anti-thrombotic drug, with highly potent activity on the coagulation mechanism. It is orally administered and rapidly absorbed and it inhibits specifically and reversibly the central point of the coagulation cascade, Factor Xa. All the published studies demonstrated that rivaroxaban has a predictable pharmacokinetic and pharmacodynamic profile, thus allowing for a fixed dose regimen. There are no metabolic products of the product in the plasma and there is no unexpected accumulation of drug concentrations upon multiple dosing, and peak plasma concentrations are reached 2-4 hours after oral administration in healthy volunteers. Cardio-vascular and hepatic side effects were similar to other anti-thrombotic drugs. There is also a low risk of bleeding. The studies conducted demonstrate that Rivaroxaban is well tolerated and effective in prevention of thrombembolic events.

Keywords: thrombo-prophylaxis, oral anti-thrombotics, Rivaroxaban.

PRIMELE REZULTATE IN TROMBO-PROFILAXIA CU NOI ANTICOAGULANTE ORALE - RIVAROXABAN

Rezumat

Rivaroxabanul este un anti-trombotic recent introdus în practica curentă, cu activitate puternică asupra mecanismului coagulării. Este administrat oral şi rapid absorbit şi inhibă specific şi reversibil punctul central al cascadei coagulării, Factorul Xa. Toate studiile publicate arată faptul că Rivaroxaban are un profil farmacocinetic şi farmacodinamic predictibil, permiţând astfel administrarea unei doze fixe. Nu există produşi de metabolism liberi în plasmă şi nu există riscul creşterii cumulative a concentraţiei plasmatice după administrări multiple; concentraţia plasmatică maximă se obţine la 2-4 ore după administrarea orală (la voluntari sănătoşi). Reacţiile adverse hepatice şi cardio-vasculare sunt similare altor anti-trombotice. Riscul de sângerare decelat a fost mic. Toate studiile au arătat că Rivaroxaban este bine tolerat şi eficient în prevenirea accidentelor trombo-embolice .

Cuvinte cheie: trombo-profilaxie, anti-trombotice orale, Rivaroxaban.

INTRODUCTION

Venous thrombosis represents by itself and by its complications, especially the embolic ones, a major cause of morbidity and mortality.

Thrombosis is initiated by an abnormal activation of the coagulation cascade, that is why the drugs currently used in prophylaxis and treatment of thrombosis are those effective in different steps of this cascade [1]. Unfractioned Heparin (UFH) is still used but mainly in the treatment of thrombosis, and less in thrombo-prophylaxis. The current standard in thrombo-prophylaxis, especially in major orthopedic surgery, which is unanimously recognized as a high thrombo-embolic risk one, is represented by Low

Articol intrat la redacţie în data de: 16.02.2010
Primit sub formă revizuită în data de: 06.04.2010
Acceptat în data de: 07.04.2010
Adresa pentru corespondenţă: olivera_lupescu@yahoo.com

Molecular Weight Heparins (LMWH), since they reduce most of the undesired effects of UFH (2). Fondaparinux sodium, which indirectly affects Factor Xa, proved to have a high risk of bleeding and Vitamin K Antagonists (VKA) have a nonspecific mechanism of action, a slow onset and offset of anticoagulating activity, and a narrow therapeutic window, patients requiring frequent laboratory monitoring [3].

New oral anti-coagulants have been created in order to respond to the major demands of higher specificity and of predictable response after a fixed unique oral dose with less bleeding risk. It is well known that the central role in the coagulation cascade is played by Factor Xa, since the inhibition of one single molecule of Factor Xa produces the inhibition of 50 molecules of thrombin [4].

Rivaroxaban directly binds to human Factor Xa, binding is specific and competitive, with more than 10 000-fold greater selectivity than for other serine proteases. It rapidly and reversible inhibits both free and fibrin-bound Factor Xa (without antithrombin as a cofactor), as well as the prothrombinase complex, but is has no direct effect on thrombin activity or platelet aggregation [5].

After oral administration, rivaroxaban is rapidly absorbed, with Cmax reached within 2–4 hours after; it has a plasma protein binding of 92–95% and it is two-thirds metabolized, so there are no major or active circulating metabolites. It is one-third excreted as unchanged active substance in urine and of the two-thirds metabolized, half is eliminated renally and half is eliminated by faecal route. No dose adjustment is necessary in patients with mild or moderate renal impairment. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk and it may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy [6].

The efficiency and safety of Rivaroxaban were the objectives of the RECORD (**RE**gulation of **C**oagulation in major **O**rthopedic surgery reducing the **R**isk of **D**VT and PE) I, II, III and IV studies which evaluated these parameters of a fixed daily dose of 10 mg of rivaroxaban as thrombo-prophylaxis after hip and knee arthroplasty [7,8,9,10].

This study presents our experience regarding the prevention of thrombembolic events using rivaroxaban as Xarelto (10 mg rivaroxaban per tablet)

MATERIAL AND METHOD

This prospective study evaluated 26 patients, who were operated in our Clinic for total hip arthroplasty between 01.06.2009 and 01.11.2009 who received Xarelto (rivaroxaban 10 mg) as thrombo-prophylactic agent. The group included 18 females and 8 males, with ages between 44 and 78 years (mean age 62 yrs) (Fig. 1).

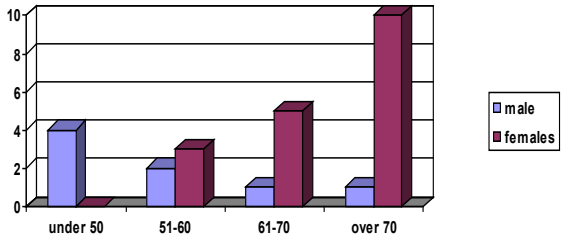

Figure 1. The group of patients – age and gender.

The patients were operated for hip osteoarthritis (OA), which was primary (16 cases- 10 females, 6 males) and secondary (10 cases - 4 females, 6 males).

Form the 16 patients with primary OA, the involvement of the hip was unilaterally in 11 patients (9 females, 2 males) and bilaterally in 5 patients, all females, while in the "secondary OA group" the involvement was unilaterally in 6 cases (4 males, 2 females) and bilaterally in 4 cases (2 males, 2 females) (Table 1).

Table 1. Etiology of the OA in the studied group.

Type of OA	males	Females	Total
Primary unilaterally	9	2	11
Primary bilaterally	0	5	5
Secondary unilaterally	4	2	6
Secondary bilaterally	2	2	4
Total	15	11	26

The etiology in group with secondary OA was:

- avascular necrosis of the femoral head – 3 cases, all males. In 2 cases, the involvement was unilaterally (and from these cases, 1 patient had had core decompressive femoral head drilling 10 years ago, then hemiarthroplasty with bipolar hip prosthesis 7 years ago) and in 1 case the disease was bilaterally; the patient had had core decompressive femoral head drilling 15 years ago and bipolar prosthesis 8 years ago on the study-side and femoral drilling 4 years ago on the opposite side, which know rapidly evolved to osteoarthritis);
- ankilosing spondilitis - 1 female, 44 yrs, with no previous surgery;
- trauma - 3 cases , all unilaterally: 1 female , 56 yrs, operated 5 years before for posterior-superior dislocation of the hip with fracture of the posterior wall of the acetabulum, stabilized with reconstruction plate and screws; 2 males (51 yrs and 43 yrs., respectively with femoral neck fractures operated with screws 4 years before and, respectively, 6 years before;
- congenital dysplasia of the hip - 1 female, 54 years, with no previous surgery, and
- cortisone therapy - 2 females with rheumatoid arthritis - the first, 66 yrs, with no previous surgery, and the other, 57 yrs, with contralateral total hip arthroplasty 3 years ago.

Pre-operative all the patients followed the same protocole:

I. Standard pre-operative evaluation, consisting of:

a. anamnesis in order to establish complete medical history, which offered significant elements in 22 patients: arterial hypertension (6 patients), ischemic coronary disease (7 cases), atrial fibrillation (2 patients), allergic reaction to penicillin (1 patient), diabetes mellitus (2 patients), arterial occlusive disease (1 patient), gout (1 patient). None of the patients had had clinical evidence or medical history for deep vein thrombosis or pulmonary embolism, nor for liver or renal impairment. None of the patients received anti-coagulants in the last 6 months prior to surgery, but 6 patients received chronic treatment with Low-Dose – Aspirin 325 mg (2 for atrial fibrillation and 4 for ischemic coronary disease), which was not considered as contra-indication for post-operative prophylaxis with Rivaroxaban;

b. clinical examination - none of the patients had clinical signs of DVT or Pulmonary Embolism, but 17 patients had varicose veins;

c. paraclinical evaluation - ECG, pulmonary radiography examined by the radiologist, lab tests for blood (hemoleucogram, serum glucose, urea, creatinine, ionogramme, liver function tests, proteins, albumin, CK (creatin-kinase), LDH (lactic-dehydrogenase/, alkaline phosphatase, ESR (erythrocyte sedimentation rate), fibrinogen, coagulation tests) and urine (biochemical and cellular evaluation and bacteriologic exam);

d. pre-operative evaluation by the anesthetist, who established specific evaluations which were addressed to previous medical history alone;

e. None of the patients received pre-operative drugs for thrombo-prophylaxis; non-specific anti-thrombotic measures were applied (proper hydration, elastic stocks for the patients with varicose veins).

Surgery was performed under spinal anesthesia in 20 patients and general anesthesia in 6 cases (due to severe degenerative changes of the spine of the patients); antibiotic treatment was administered to the patients at induction:

- cephalosporin with aminoglycosides in 8 cases
- cephalosporin alone in 3 cases
- quinolone with aminoglycosides in 7 cases
- quinolones alone in 2 cases
- quinolones with glycopeptides in 5 cases

Lateral hip approach was performed in all the cases, except 1 case, when the posterior approach was used because it had had been previously used for stabilizing the fracture of the posterior wall.

The type of the prosthesis was chosen depending the known criteria: age, the quality and the quantity of bone (bone capital). The correlation between age and the type of the prosthesis is represented in Figure 2.

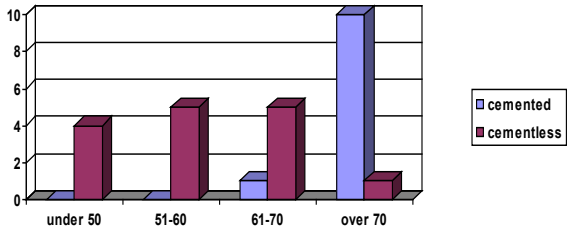

Figure 2. Correlation between age and the type of prosthesis.

Active suction was used during surgery in order to evaluate blood loss and **Intraoperative Red Blood-Cell Salvage**-Reinfusion System (so called "Cell Saver") was used in 10 of the 16 cases; intra-operative blood loss was 620-1050 ml (mean value 785 ml) (Figure 3).

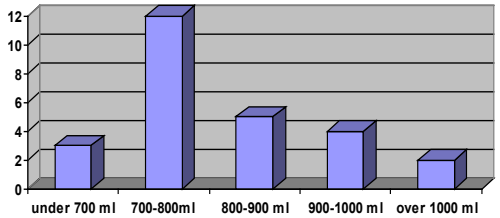

Figure 3. Blood loss during surgery.

There were two types of re-infusion performed:

- all the intra-operative blood was collected and processesed and reinfused at the end of the operation (usually, after fascial suture) – this method was used when intra-operative blood loss did not exceed 800 ml, or

- when the intra-operative blood loss reached 800 ml, this quantity was processed and reinfused; meantime the rest of the quantity was collected and reinfused after surgery was finished.

Besides the reinfused blood, transfusion with total blood or RBC (red blood cells) was performed intra-operative in 11 cases (6 cases operated without reinfusion system and 5 cases when reinfusion system was used, but intra-operative blood loss was more than 500 ml before finishing the acetabular preparation).

Active drainages (adjacent to the prosthesis and subfascial) were installed and post-operative blood loss was monitored in order to establish the moment of starting thrombo-prophylaxis. Elastic bilateral stockings were used at the end of surgery in all the patients.

Rivaroxaban 10 mg daily (fixed dose) was given to the patients, starting after a mean time of 9.2 hrs post-operative, since in all the patients it was provided that haemostasis has been established. The moment of first administration was between 8-10 hours post-operative, depending on the post-operative drainage.

Post-operative monitoring of the patients during hospitalization consisted in:

1. clinical evaluation: daily (and whenever it was considered necessary) general examination, thorough evaluation of the legs and wound surveillance following local standards, with drainage removal 48 hrs after surgery;

2. standard laboratory tests: the same complete pre-operative tests were performed routinely in the evening of the operation day (4-6 hours after the end of the suture) and in the next morning;

3. Hemoleucograms and coagulation tests were performed for all the patients at discharge;

4. The patients were instructed to come for control for suture removal, then 35-42 days after surgery;

5. Compression ultrasound was planned to be performed to all the patients at discharge (which was after a mean time of 9.5 days in this group of patients, from 8-12 days), then 35-42 days after surgery (when the treatment with rivaroxaban was stopped) and whenever it was considered to be necessary due to clinical signs of DVT (Deep Venous Thrombosis).

RESULTS

All the patients received rivaroxaban for 35-42 days after surgery (mean time 38.3 days), no discontinuation of the treatment was described in the study group.

From the studied group, 3 patients developed persistent oedema of the operated leg; all of them after more than 3 weeks from surgery (after 25, 31 and 33 days correspondingly). Doppler compression ultrasound was performed and it detected thrombosis of the peroneal veins in one of the patients, who came for control 35 days after surgery (2 days after oedema onset), so Xarelto was anyway stopped, venography was performed and it detected thrombosis in the peroneal veins, but also in the anterior tibial veins, so Unfractioned Heparine (UFH) treatment of DVT was started, following known protocols.

Doppler Compression Ultrasound was performed at 2, 4, 8 and 12 weeks after Heparine treatment was started and it showed progressive reduction of the thrombus until 12 weeks, when it completely disappeared. Venography was then performed and it also revealed complete thrombi removal.

For the other two patients with oedema, it was explained (by compression ultrasound) by chronic venous insufficiency. It is to be underlined that all the three patients had varicose veins before surgery.

One of the patients developed an acute episode of dispneea (suspicion of pulmonary embolism) 3 days after surgery, together with increased blood pressure (arterial hypertension in medical history); lab tests (especially D-dimers), ECG and CT scan excluded pulmonary embolism, so acute cardiac failure due to hypertensive crisis was considered to be the cause for dispneea. Specific treatment was given to the patient and the outcome was favorable

Post-operative bleeding was within the recognized standards (600-1300 ml, with a mean value of 715 ml) and blood was given post-operative (1- 4 units) depending on the hemograme The variation of the Hemoglobin is shown in Figure 4.

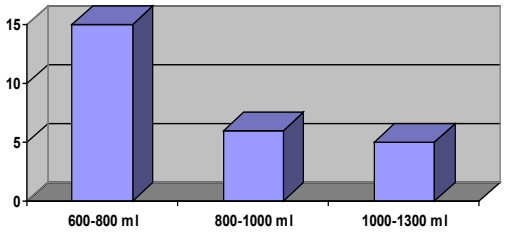

Figure 4. Post-operative blood loss.

Post-operative values of hemoglobin were compared to those pre-operative and the difference was monitored. The differences were:

a. for the tests performed in the day of surgery: between the highest: 4.0 grams/100 ml and the lowest 1.2 grams/100 ml (mean value 2.4 g/100 ml). Post-operative transfusions were indicated in the cases when the value of hemoglobin was less when this differences exceeded 2 g/100 ml or when the absolute value was less than 9 g/100 ml;

b. for the tests performed the second day, the difference was (compared to the post-operative value) between 0.72 g/100 ml and 2.4 g/100 ml (mean value 1.1 g/100 ml);

c. for the tests performed the second day.

None of the patients developed post-operative bleeding, not at the surgical wound site, either in different organs and systems, and no major bleeding (defined as life threatening bleeding or a bleeding which required reintervention) was detected.

One of the patients developed an acute allergic reaction to Paracetamol, which had no relation to rivaroxaban and did not interfere with its administration (Figure 5).

Complete paraclinical evaluation (lab tests) were performed corresponding to the local standard procedures (routine post-operative tests, then second day routine tests), only repeated if the patients had post-operative anemia and needed blood transfusions. No supplementary evaluation of coagulation was necessary, none of the patients developed thrombocytopenia during these standard tests appeared.

Liver and renal function tests were modified at 12 patients in the post-operative set, from these only 4 had these tests modified the second day, while they became normal for all the patients at discharge. None of these tests were reasons for stopping the treatment, so we concluded that no impairment of liver or renal function appeared during the treatment with Rivaroxaban, no need to interfere with the anti-thrombotic treatment due to other side effects.

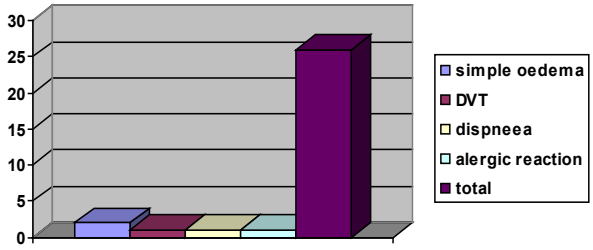

Figure 5. Clinical outcome - adverse events.

DISCUSSION

The problem of thrombo-embolic complications after major orthopedic surgery is still debated, since none of the until-now-described methods managed to completely overrun the risk of these complications.

Rivaroxaban, a new oral anticoagulant has two major advantages: the oral administration and the fixed dose, no matter weight or associated diseases. For the moment, the indications for thrombo-prophylaxis with rivaroxaban are represented by elective surgery of the hip (total hip replacement) and knee [11].

Our experience with rivaroxaban is still at the beginning that explains the relatively small number of the patients who were monitored as described before.

The data obtained from the patients mentioned above confirmed those from the RECORD studies, which are quite optimistic when analyzing the risk-benefit ratio for rivaroxaban .

The problems which are to be discussed from the above - presented aspects are the following:

It is very important for succeful thrombo-prophylaxis with rivaroxaban in hip arthroplasty to respect the long-time prophylaxis rule, which, according to literature consistently reduces the incidence of thrombo-embolic events [12].

The problem whether to start thrombo-prophylaxis before or after surgery has not been concluded, yet. There is no consensus concerning the moment of starting VTE prophylaxis, and none of the two methods (pre-operative- or post-operative initiation of prophylaxis) proved to be clearly superior. If pre-operative prophylaxis is intended, LMWH are to be chosen, since the indications of rivaroxaban are restricted to post-operative thrombo-prophylaxis. The distance between closure of the surgical wound and rivaroxaban administration has to be at least 8 hours, in order to allow the coagulation mechanism to achieve haemostasis, since the rule is to start administering rivaroxaban if hemostasis is proven to have been achieved. This term indicates that the surgeon has to be sure that no active bleeding exceeding normal is at the wound site, otherwise the administration of any anti-thrombotic drug is prohibited. This rule is valid for all the products used for thrombo-prophylaxis, the only difference is the time between wound closure and first administration [13].

The relatively low rate of thrombosis in the study group and the other results are not to be compared to those obtained in the RECORD studies since there is a considerably difference between the designs of the studies and the timetables of the visits

The results obtained in the study group demonstrates that no adjacent laboratory tests were necessary in order to monitorise the patients; this fact can indicate that standard evaluation of the patients is enough when rivaroxaban is administered.

In the studied group there were no side events and the tolerability of Rivaroxaban was very good. There were no cases of liver and renal impairment, and no gastro-intestinal disturbance was described, thus indicating that it is possible to reduce the risk of these unpleasant events using rivaroxaban.

CONCLUSIONS

For a successful thrombo-prophylaxis, it is important to thoroughoully evaluate the patient in order to identify all the risk factors and to use the proper methods. The anti-coagulants were continuously improved in order to obtain efficacy, safety, specificity, tolerability and a convenient administration. This analyses, even if performed on a small group of patients, demonstrated that rivaroxaban (Xarelto) demonstrated to be effective and safe, being orally administered. No side effects were described in the study group, so we can conclude that the drug is characterized by a good tolerability. Until its indications will become wider, the until-now established indications of rivaroxaban makes it an efficient thrombo-profilactic agent to be used in major orthopedic surgery.

References

1. Esmon C.: Basic mechanisms and pathogenesis of venous thrombosis. Blood Reviews, 2001, 23, 225-229

2. Samama C., Gigou F.: Low-Molecular-Weight Heparin vs. Unfractionated Heparin in Femorodistal Reconstructive Surgery: A Multicenter Open Randomized Study, Annals of Vascular Surgery, 2002 , 9, 845-853

3. Mismetti P., Laporte S., Zufferey P.: Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis, J Thomb Haemostasis 2002, 2, 1058-1070

4. Philippe C.: Selective Factor Xa Inhibition Improves Efficacy of Venous Thromboembolism Prophylaxis in Orthopedic Surgery, Thrombosis Research 2007, 3, 205-212

5. Duggan T., Scott J., Plosker L.: Rivaroxaban: A Review of its Use for the Prevention of Venous Thromboembolism After Total Hip or Knee Replacement Surgery, Drugs 2009. 69(13), 1829-1851

6. Rohde G.: Determination of rivaroxaban – a novel, oral, direct Factor Xa inhibitor – in human plasma by high-performance liquid chromatography–tandem mass spectrometry Drug Metabolism and Pharmacokinetics, Bioanalytics, Bayer HealthCare AG, Aprather Weg, 42096 Wuppertal, Germany

7. Erksson B. I., Borris L., friedman R.J., Haas S. Huisman M.V., Kakkar A.K., et al.: Rivaroxaban versus Enoxaparin for

Thromboprophylaxis after Hip Arthroplasty, N Engj J Med 2008, 358, 2765-2775
8. Kakkar A.K., et al; RECORD 2 Investigators : Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty , Lancet 2008, 372, 1-9.
9. Lassen M.R., Ageno W., Borris L.C, et al; RECORD3 Investigators: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty, N Engl J Med. 2008;358(26), 2776-2786..
10. Turpie A.G., Lassen M.R., Davidson B.L., et al; RECORD4 Investigators : Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial, Lancet. 2009, 373(9676):1673-1680
11. Eriksson B.I., Borris L., Dahl O.E et al: Oral, direct Factor Xa inhibition with BAY 59–7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemos,. 2006a;4,121–8
12. Eriksson B. I., Kakkar A. K., Turpie A. G. G., Gent M., Bandel T.-J., Homering M. et al.: Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement, J Bone Joint Surg Br 2009 91-B, 636-644
13. Van Thiel D., Kalodiki E., Wahi R., Litinas E., Haque W., Rao G.: Interpretation of Benefit-Risk of Enoxaparin as Comparator in the RECORD Program: Rivaroxaban Oral Tablets (10 milligrams) for Use in Prophylaxis in Deep Vein Thrombosis and Pulmonary Embolism in Patients Undergoing Hip or Knee Replacement Surgery, Clin Appl Thromb Hemost 2009, 15, 389-394