CARDIOVASCULAR MEDICINE

Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol

I Ferreira, L Dos, P Tornos, I Nicolau, G Permanyer-Miralda, J Soler-Soler

Heart 2003;**89**:527–530

See end of article for authors' affiliations

Correspondence to: Dr I Ferreira González, Cardiology Department, Hospital Universitari Vall d'Hebron, Pge Vall d'Hebron 119-129, 08035 Barcelona, Spain; 32453ifg@comb.es

Accepted 20 November 2002

Objectives: To evaluate the incidence of thromboembolic and haemorrhagic events in a cohort of patients with mechanical heart valves who had to withhold acenocumarol and were treated with enoxaparin.
Design: Observational prospective study.
Setting: In hospital; after discharge, and follow up by telephone call.
Patients and methods: All consecutive patients with mechanical heart valves admitted to the authors' hospital between May 1999 and January 2002 who had to interrupt treatment with acenocumarol and were treated with enoxaparin as an alternative to other methods were enrolled. In each patient, the following characteristics were prospectively determined: the reason for interrupting acenocumarol, demographic data, estimated global risk for thromboembolic events, international normalised ratio before starting enoxaparin treatment, number of days taking enoxaparin, and mean level of anti-Xa activity during treatment. All patients were followed up through clinical history during the hospitalisation and by telephone after discharge to detect thromboembolic events.
Main outcome measure: Presence of thromboembolic or haemorrhagic events.
Results: 82 patients were identified and followed up for a mean of 2.8 months (range 1.5–3.5 months) after discharge. 61 of them (74%) had one or more associated thromboembolic risk factors. Acenocumarol was interrupted (to perform an invasive procedure in 74 patients and because of haemorrhagic complication in 8) an average of 11.2 days (range 3–40 days). Most patients received the standard enoxaparin dose (1 mg/kg at 12 hour intervals). Mean (SD) anti-Xa activity was 0.58 (0.3) IU/ml (median 0.51). There were 8 minor and 1 major bleeding events during enoxaparin treatment. No thromboembolic complications were clinically detected during hospitalisation or during follow up (95% confidence interval 0% to 3.6%).
Conclusions: Enoxaparin may be an effective and relatively safe substitute anticoagulant for patients with mechanical heart valves who must withhold acenocumarol.

The management of anticoagulation in patients with a prosthetic heart valve can be especially difficult in two clinical situations: in patients who must withhold antithrombotic treatment before and after an invasive procedure, and in those who have a bleeding complication while receiving acenocumarol. Although low molecular weight heparins (LMWH) are an attractive alternative to other anticoagulant strategies because of their pharmacokinetic and pharmacodynamic properties,[1] there is not enough clinical evidence to consider their effectiveness and safety to be definitive in both mentioned settings.

This observational prospective study was carried out on a cohort of patients with prosthetic heart valves and various thromboembolic risk factors. These patients were admitted to our hospital in several clinical situations that led to interruption of treatment with acenocumarol and were treated with enoxaparin as an alternative to other methods.

PATIENTS AND METHODS

Study population

We studied 82 consecutive patients with prosthetic heart valves admitted to hospital between May 1999 and January 2002 who had to interrupt treatment with acenocumarol because of a bleeding complication or because they had to undergo specific procedures considered to be of moderate or high bleeding risk. All of them received enoxaparin instead of unfractionated heparin as antithrombotic treatment. In each patient, the following characteristics were prospectively determined:

- reason for interrupting acenocumarol
- demographic details
- global risk for thromboembolic events
- international normalised ratio (INR) just before starting enoxaparin
- number of days with enoxaparin and mean anti-Xa activity level during treatment
- presence of thromboembolic or haemorrhagic events during hospitalisation and follow up.

Definitions

According to American College of Cardiology/American Heart Association Task Force guidelines, patients who had had a recent thrombosis or embolus (arbitrarily within one year), those with evidence of thrombotic problems when previously they were not receiving anticoagulant treatment, those with the Björk-Shiley valve, and those with two or more risk factors or with a mitral prosthetic valve and one risk factor were considered to have a high risk for having a thromboembolic event periprocedure. Atrial fibrillation, previous thromboembolism, a hypercoagulable condition, and left ventricular dysfunction (ejection fraction < 0.3) were considered to be risk factors.[2] Patients with a Starr-Edwards mechanical valve (old model of cardiac valve) were also included as being high risk patients, according to other studies.[3]

INR was measured within the first hours after admission and just before starting treatment with enoxaparin. INR was judged as correct if it was in the target range, or incorrect if it

Table 1 Patient demographics, type and position of prostheses, and international normalised ratio (INR) required

	Number
Male sex	51
Age (mean (SD))	64 (11)
Renal impairment	11 (13%)
Prosthesis position	
Aortic	43 (52%)
Mitral	24 (29%)
Mitral and aortic	13 (16%)
Mitral and tricuspid	2 (3%)
Type of prosthesis	
Sorin Bicarbon	29 (35%)
Carbomedics	27 (33%)
Björk-Shiley	22 (27%)
Medtronic-Hall	3 (4%)
Starr-Edwards	1 (1%)
INR required*	
2–3	21 (25%)
2.5–3.5	61 (75%)

*Depending on the type and position of the prosthesis and additional thromboembolic risk factors (see table 2).

was not, according to recent published recommendations in managing oral anticoagulation.[4]

Classification of bleeding events was established following two categories: minor events (reported but not requiring additional testing, referrals, or visits); and major events (fatal or life threatening bleeding episodes or bleeding with a defined drop in haemoglobin concentration, leading to transfusion or to hospitalisation).[5] Patients who were in hospital for haemorrhagic complications (such as retroperitoneal haemorrhage), and thus not attributable to enoxaparin, were not considered to have bleeding events.

Enoxaparin management

Enoxaparin management during hospitalisation depended on the specific reason for interrupting acenocumarol and renal function status. Patients with correct renal function who had to undergo major surgery or an invasive procedure with bleeding risk received, once the INR became subtherapeutic (below 1.5), the standard dose of 1 mg/kg enoxaparin subcutaneously at 12 hour intervals to get an anti-Xa activity level in the therapeutic range of 0.5–1 IU/ml, as previously defined in other studies.[6] If their renal function was impaired, with creatinine concentration $\geqslant 1.5$ mg/dl ($\geqslant 133$ μmol/l), they received the lowest dose of enoxaparin required to get an anti-Xa activity level above 0.4 IU/ml (the dose administered was reduced empirically and adjusted to the level of anti-Xa activity).[7] In both cases, enoxaparin was withheld 12–18 hours before the procedure and restarted at the same dose and frequency after the procedure once haemostasis was achieved.[8] In patients admitted to hospital for a bleeding episode, acenocumarol was interrupted and vitamin K was administered if necessary and enoxaparin was started at the recommended prophylactic dose of 40 mg at 24 hour intervals once INR became subtherapeutic (below 1.5). Such a dose of enoxaparin was maintained until haemostasis was achieved and the risk of new episodes was judged to be low, after which the standard dose of 1 mg/kg was given at 12 hour intervals. In all cases acenocumarol was restarted a few days before discharge at the patient's usual dosage and enoxaparin was stopped when INR became > 1.5.

Follow up

All patients were followed up by clinical history to detect thromboembolic or haemorrhagic events during hospitalisation. Considering that the thromboembolic rate is higher in the first three months after surgery,[9] all patients were followed up by telephone after discharge during which a clinical anamnesis directed to detect thromboembolic events was conducted.

Table 2 Thromboembolic risk factors

	Number
Aortic prosthesis with no other risk factor	21 (26%)
Aortic prosthesis plus one risk factor	10 (12%)
AF	2
Previous thromboembolism	1
Björk-Shiley valve	6
Recent thrombosis or embolus	1
Aortic prosthesis plus two risk factors	10 (12%)
AF and previous thromboembolism	3
AF and hypercoagulable condition	1
AF and Björk-Shiley valve	5
AF and Starr-Edwards valve	1
Aortic prosthesis plus three risk factors	2 (2%)
AF, previous thromboembolism, and EF <30%	1
AF, Björk-Shiley valve, and previous thromboembolism	1
Mitral prosthesis with no other risk factor	6 (7%)
Mitral prosthesis plus one risk factor	13 (16%)
AF	11
Thrombotic event when previously not taking treatment	1
Recent thrombosis or embolus	1
Mitral prosthesis plus two risk factors	14 (17%)
AF and previous thromboembolism	6
AF and EF <30%	1
AF and Björk-Shiley valve	5
Björk-Shiley valve and previous thromboembolism	1
Björk-Shiley valve and EF <30%	1
Mitral prosthesis plus three risk factors	6 (7%)
AF, EF <30%, and previous thromboembolism	2
AF, hypercoagulable condition and previous thromboembolism	1
AF, Björk-Shiley valve, and previous thromboembolism	3
Total	82

AF, atrial fibrillation; EF, ejection fraction.

Table 3 Specific reason for interrupting acenocumarol in each patient

	Number
Invasive procedures (n=74)	
Cardiac surgery (n=26)	
Mitral valve replacement	2
Mitral and tricuspid valve replacement	1
Aortic valve replacement	1
Aortic coarctation repair	1
Pacemaker implantation	20
Coronary surgery	1
Cardiac catheterisation (n=15)	
Abdominal and general surgery (n=7)	
Cholecystectomy	2
Thyroidectomy	1
Umbilical hernioplasty	1
Repair of anal fistula	2
Parotidectomy	1
Vascular and thoracic surgery (n=6)	
Repair of femoral pseudoaneurysm	1
Thoracocentesis	4
Tracheal surgery	1
Endoscopic procedures (n=4)	
Gastric biopsy	1
Polipeptomia	2
Ureteroscopy	1
Urological surgery (n=3)	
Transurethral prostatic resection	1
Transurethral resection of vesical tumour	1
Suprapubic prostatectomy	1
Orthopaedic surgery (n=2)	
Osteosynthesis for trauma	2
Plastic surgery (n=1)	
Others (n=10)	
Hepatic biopsy	1
Testicular biopsy	1
Subclavian catheterisation	4
Paracentesis	1
Pregnancy	1
Aspiration puncture	1
Cholecystography	1
Haemorrhagic complications (n=8)	
Retroperitoneal bleeding	1
Gastrointestinal tract bleeding	5
Urinary tract bleeding	1
Intracranial bleeding	1

Anti-Xa measurement

Anti-Xa activity was measured six hours after the injection of enoxaparin. The first measurement was taken within three days after enoxaparin was started and was followed by new measurements at 3–5 day intervals (depending on the level of anti-Xa activity). Nine parts of freshly drawn venous blood were collected into one part trisodium citrate and centrifuged at 2000 *g* for 10–20 minutes at 20–25ºC. The anti-Xa activity of enoxaparin was measured with a colorimetric assay with a synthetic chromogenic substrate (Chromogenix-Instrumentation Laboratory, Milan, Italy).

RESULTS

Tables 1 and 2 show patient demographics, the target INR in each patient depending on the type and position of the prostheses, and the presence of additional thromboembolic risk factors. Only 21 patients (26%) could be considered to have low thromboembolic risk—that is, those with mechanical heart valve (not Björk-Shiley or Starr-Edwards valves) in the aortic position, without any other associated thromboembolic risk factor. The remaining 61 (74%) had one or more thrombogenic conditions that required the use of anticoagulant substitutive treatment once INR became subtherapeutic.[2] Thirty two patients (39%) had an especially high risk of thromboembolism: those with mechanical heart valve in the aortic or mitral position and two or more associated risk factors. The most frequent associated thromboembolic risk factor was atrial fibrillation, which was present in 42 patients (52%).

The most frequent reason for stopping acenocumarol in the 82 patients with mechanical heart valves who were in hospital in the period of the study was to perform an invasive procedure with bleeding risk, specifically pacemaker implantation (20 (24%) of all procedures; table 3). Only eight patients (10%) were admitted to hospital for a primary bleeding episode during acenocumarol treatment; two of them required transfusion and administration of vitamin K. Among these patients who were in hospital because of primary bleeding, only one had a low risk of thromboembolism, two had a moderate risk with a Björk-Shiley valve in the aortic position but without any other thromboembolic risk factor, and the remaining five had a high risk of thromboembolism.

INR was within therapeutic range just before starting enoxaparin in 64 patients (78%). Enoxaparin was maintained an average (SD) of 11.2 (6.8) days (range 3–40 days). Anti-Xa activity was measured in 67 patients; the mean (SD) anti-Xa activity during treatment was 0.58 (0.3) IU/ml (median 0.51 IU/ml). There were nine (11%) bleeding events during hospitalisation, eight minor events and one major event, all of them during enoxaparin treatment: six patients developed postprocedure bleeding complications (all soft tissue bleeding that did not require transfusion), one patient developed epistaxis, and two patients developed urinary tract bleeding, one of them requiring transfusion. The mean (SD) follow up was 2.8 (0.85) months (range 1.5–3.5 months). No thromboembolic complications were clinically detected either during hospitalisation or during follow up.

DISCUSSION

In the particular setting of the performance of a procedure with bleeding risk in patients with prosthetic heart valves, once acenocumarol is interrupted and INR becomes subtherapeutic, patients have a high risk of thromboembolic complications depending on patient associated risk factors (including type and position of prostheses) and procedure associated risk. For this reason anticoagulant management can be difficult during such a period. Classically, four options for anticoagulation management have been considered in this setting: firstly, continued use of oral anticoagulation; secondly, discontinuation of oral anticoagulation without replacement parenteral anticoagulation; thirdly, discontinuation of oral anticoagulation with full dose replacement parenteral anticoagulation; and lastly, discontinuation of oral anticoagulation with low dose replacement parenteral anticoagulation.[1] Although the use of enoxaparin in this clinical context has been recently incorporated in guidelines of clinical practice, with a level of recommendation of 2C,[5] reported studies are insufficient to establish its safety and effectiveness.[6 8 10–14] The most important study that has evaluated the use of enoxaparin in this clinical scenario was a comparative, non-randomised study in 208 consecutive patients who underwent a single or double heart valve replacement with mechanical prostheses and were anticoagulated with unfractionated heparin in the first period and enoxaparin in the second phase.[6] This study showed that enoxaparin in the high risk postoperative period is at least as safe and effective as unfractionated heparin.

In another clinical scenario (patients with prosthetic heart valves admitted to hospital for a primary bleeding complication during acenocumarol treatment) the general management involves attempting to identify and reverse the cause of bleeding and maintaining the INR at the lower limit of the therapeutic range.[5] However, there are no data on the use of LMWH in this clinical situation. The risk of thromboembolic complications in this case depends mostly on patient associated risk factors.

In past years, anticoagulation management in patients with a mechanical heart valve, who were admitted to our hospital for several reasons that led to interruption of acenocumarol, has included the use of enoxaparin following the above mentioned protocol. Our aim in this study was to evaluate the effectiveness and safety of enoxaparin in 82 consecutive patients who were anticoagulated following such a protocol. We have found two reasons for interrupting acenocumarol in this setting: the performance of specific procedures with bleeding risk and, much less frequently, hospitalisation for a primary bleeding complication during oral anticoagulation.

Considering only the type and position of the prostheses, the population of our study was, mostly, a high risk one for thromboembolic complications. In fact, in the largest study with newer generation valves, the most important predictive factors for adverse outcomes (bleeding and thromboembolic events) after non-cardiac surgery in patients with a mechanical heart valve were the type of mechanical valve (higher risk in tilting disk valve (odds ratio 5.65)), location of heart valve (higher risk in mitral position (odds ratio 3.17)), and type of surgery (higher risk in malignant tumour surgery).[15] Considering only these approaches, 61% of the patients in our cohort had a high risk of thromboembolism. In addition, 67% of the patients had another associated thromboembolic risk factor (particularly atrial fibrillation, which associated with mitral valve disease leads to an 18-fold increase in embolic risk)[9]; thus, we can consider our population to be at a high risk for thromboembolic complications. As regards procedure associated risk, all procedures in our cohort can be considered to have only a moderate risk of thromboembolism.

Another study showed that the thromboembolic rate is highest in the first three months following surgery—20% of all thromboembolic complications occur during the first month, when a pronounced hypercoagulable state is present, which decreases with time.[16] Despite the high global risk of thromboembolism in our cohort, no thromboembolic event was detected either during hospitalisation or after a mean of 2.8 months of follow up. Although the follow up method may have limitations in detecting all thromboembolic events (particularly valve thrombosis), we think it is sensitive enough to detect those with clinical expression, who are the ones reported on in the literature. If we apply the rule of three to our results,[17] the 95% confidence interval for the rate of thromboembolic events is 0% to 3.6%. This interval does not wholly exclude the possibility of a significant rate of thromboembolic complications, although this seem unlikely; therefore, wider studies are justified on the basis of our findings.

As regards safety of enoxaparin, only one substantial haemorrhagic complication attributable to enoxaparin was observed, maybe because most procedures performed in our series were not of high haemorrhagic risk or because the mean anti-Xa activity levels were in the lower limit of the therapeutic range (95% of patients had anti-Xa activity < 1.1 IU/ml). In fact, the highest anti-Xa activity in patients who bled during enoxaparin treatment was 1.1 IU/ml.

This report details our experience to date using enoxaparin in patients with prosthetic heart valves. The number of patients and the study design, however, did not allow us to reach conclusions about the effectiveness and safety of using enoxaparin compared with other methods. However, our patients were not selected and, for this reason, our data represent a real clinical practice observation of using enoxaparin in this indication. Although further randomised studies comparing the use of LMWH with this indication and the other aforementioned methods are necessary, we think that, at this time, their use in daily clinical practice can be considered.

Authors' affiliations

I Ferreira, L Dos, P Tornos, G Permanyer-Miralda, J Soler-Soler, Cardiology Department, Hospital Universitari Vall d'Hebron, Institut Català de la Salut, Barcelona, Spain
I Nicolau, Haematology Department, Hospital Universitari Vall d'Hebron

REFERENCES

1 **Shapira Y**, Vaturi M, Sagie A. Anticoagulation management of patients with mechanical prosthetic valves undergoing noncardiac surgery: indications and unresolved issues. *J Heart Valve Dis* 2001;**10**:380–7.
2 **Bonow RO**, Carabello B, de Leon AC Jr, *et al*. ACC/AHA guidelines for the management of patients with valvular heart disease: executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on management of patients with valvular heart disease). *Circulation* 1998;**98**:1949–84.
3 **Meschengieser SS**, Carlos GF, Santarelli MT, *et al*. Low-intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. *J Thorac Cardiovasc Surg* 1997;**113**:910–6.
4 **Stein PD**, Alpert JS, Bussey HI, *et al*. Antithrombotic therapy in patients with mechanical and biological prosthetic heart valves. *Chest* 2001;**119**:220S–7S.
5 **Ansell J**, Hirsh J, Dalen J, *et al*. Managing oral anticoagulant therapy. *Chest* 2001;**119**:22S–38S.
6 **Montalescot G**, Polle V, Collet J, *et al*. Low molecular weight heparin after mechanical heart valve replacement. *Circulation* 2000;**101**:1083–6.
7 **Collet J**, Montalescot G, Choussat R, *et al*. Enoxaparin in unstable patients with renal failure. *Int J Cardiol* 2001;**80**:81–2.
8 **Spandorfer JM**, Lynch S, Weitz HH, *et al*. Use of enoxaparine for the chronically anticoagulated patient before and after procedures. *Am J Cardiol* 1999;**84**:478–80.
9 **Gohlke-Bärwolf C**. Anticoagulation in valvar heart disease: new aspects and management during non-cardiac surgery. *Heart* 2000;**84**:567–72.
10 **Carrel TP**, Klingenmann W, Mohacsi PJ, *et al*. Preoperative bleeding and thromboembolic risk durtin non-cardiac surgery in patients with mechanical prosthectic heart valves: an institutional review. *J Heart Valve Dis* 1999;**8**:392–8.
11 **Galla JM**, Fuhs BE. Outpatients anticoagulation protocol for mechanical valve recipients undergoing non-cardiac surgery [abstract]. *J Am Coll Cardiol* 2000;**35**(suppl A):531.
12 **Ferreira IJ**, Dos L, Tornos MP, *et al*. Is low-molecular-weight heparin a safe alternative to unfractionated heparin in patients with prosthetic mechanical heart valves who must interrupt antithrombotic therapy? [abstract]. *Eur Heart J* 2000;**21**(suppl):301.
13 **Johnson J**, Turpie AGG. Temporary discontinuation of oral anticoagulants: role of low molecular weight heparin [abstract]. *Thromb Haemost* 2001:**86**(suppl):P2323.
14 **Tinmouth A**, Kovacs MJ, Cruickshank M, *et al*. Outpatient peri-operative and peri-procedure treatment with dalteparin for chronically anticoagulated patients at high risk for thromboembolic complications. *Thromb Haemost* 1999;**82**(suppl):662.
15 **Carrel TP**, Klingenmann W, Mohacsi PJ, *et al*. Preoperative bleeding and thromboembolic risk durtin non-cardiac surgery in patients with mechanical prosthectic heart valves: an institutional review. *J Heart Valve Dis* 1999;**8**:392–8.
16 **Butchart EG**, Bodnar E, eds. *Thrombosis, embolism and bleeding*. London: ICR Publishers, 1992:293–31.
17 **Jovanovic B**, Levy P. A look at the rule of three. *Am Stat* 1997;**51**:2,137–9.