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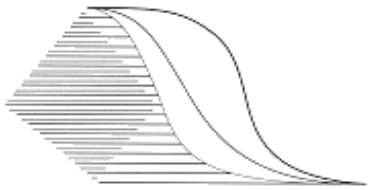

RELATIVE EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN PREPARATIONS FOR NON-HOSPITAL PROPHYLAXIS AND TREATMENT OF VENOUS THROMBO-EMBOLIC DISEASE

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Joint Health Technology Assessment Series

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Table of Contents

Introduction to the Series

The Joint Heath Technology Assessment Series reports on projects initiated by the British Columbia Office of Health Technology Assessment (BCOHTA) and evidence-based medicine programs in BC. These programs are dedicated to producing unbiased, systematic reviews of clinical efficacy and effectiveness evidence for health care providers, administrators, policy makers, and the general public, and currently include:

- Therapeutics Initiative (TI), Department of Pharmacology and Therapeutics, Faculty of Medicine, University of BC, Vancouver
- Technology Assessment Committee, Capital Health Region, Victoria
- Drug Benefit Committee, Pharmacare, and ad hoc Health Technology Assessment Committees, the Ministry of Health and Ministry Responsible for Seniors, Victoria
- Technology Assessment Committee, Workers' Compensation Board of BC, Richmond
- Population Testing Programs, Boundary Health Unit, South Fraser Health Unit, Surrey
- BC Research Institute for Child and Family Health, BC Women's and Children's Hospital, Vancouver
- Public Health Nursing, Boundary Health Unit, South Fraser Health Region, Surrey
- Centre for Clinical Epidemiology and Evaluation, Vancouver Hospital and Health Sciences Centre, Vancouver

Topics reflect initiative and institutional needs. Priority is given to topics with significant impact on patient health and health care costs, and with issues in more than one context. The goal is to teach systematic review and critical appraisal skills and coordinate efforts among geographically separate and institutionally diverse contexts.

Two different types of evidence-based medicine problems are addressed:

1. uncertainty regarding new technology
2. discrepancy between evidence and practice for established technology.

The Joint HTA Series will produce scientifically valid systematic reviews that key individuals in each receptor site support. The key individuals are needed to present and defend the systematic review conclusions during ongoing committee debates. This step is essential to connect health policy, including funding decisions, to the available efficacy and effectiveness evidence.

Relative efficacy and safety of low molecular weight heparin preparations for non-hospital prophylaxis and treatment of venous thrombo-embolic disease

1.0 Request

Pharmacare currently faces the difficult task of coordinating its non-hospital low molecular weight heparin (LMWH) reimbursement policy with the diverse reimbursement policies found among hospitals in the British Columbia.[1] As part of this coordination effort, Pharmacare asked the Therapeutics Initiative (TI) for an evidence-based opinion on the **relative** efficacy and safety of LMWH preparations. Whereas BC hospitals conduct their own literature reviews and set independent formulary policy, Pharmacare tends to turn to the TI for systematic reviews and critical appraisal expertise.

Pharmacare asked about the **relative** efficacy and safety of LMWHs because its current reimbursement policy is under review. At issue is the question of substitution. The current policy is:

1) to restrict funding of all LMWHs to known indications, as part of its Special Authority Process
2) to recommend use of the least expensive LMWH, tinzaparin
3) to accept requests for funding of other, more expensive preparations: enoxaparin and dalteparin.

In relation to this policy, Pharmacare asked TI: Is there any scientific evidence that substituting one LMWH for another results in decreased efficacy or safety? Important to note, Pharmacare acknowledges the differences in molecular structure, pharmacokinetics, and biological activity among LMWH preparations. Nevertheless, Pharmacare asked whether, despite these known differences, is there evidence that substitution diminishes patient outcome?

2.0 Background

LMWH and unfractionated heparin (UH) are glycosaminoglycans consisting of chains of alternating reisidues of glucuronic acid or iduronic acid.[2] LMWHs available in Canada are all derived, albeit differently, by de-polymerization of porcine (and perhaps in part bovine) mucosal heparin. Most LMWHs have a molecular weight of about one-third that of heparin.

The rationale for using LMWH, as opposed to UH, in humans is from animal studies that found it possible to dissociate the antithrombotic from the hemorrhagic effect of these agents.[3] In particular, LMWHs provide the opportunity to maintain the same antithrombotic effect while decreasing the hemorrhagic effect.

Animal studies comparing the antithrombotic and hemorrhagic effect of various LMWHs preparations found no significant differences among the preparations.[4,5] The studies concluded that method of preparation of LMWH did **not** influence in vivo antithrombotic activity or hemorrhagic effect.

2.1 Manufacturing

The following quotation from a recent review of LMWH pharmacology[6] summarizes the main drug manufacturing features:

> **Enoxaparin** (*Levenox*) is obtained by benzlation followed by alkaline depolymerization (beta elimination). Large amounts of sodium bisulfite are added to prevent oxidation of the terminal groups, since this product contains a double bond at the reducing end. However, a recent formulation does not contain any sodium bisulfate and the new formulation is claimed to exhibit pharmacological effects similar to those of the original product.
>
> **Dalteparin** (*Fragmin*) is obtained by nitrous acid depolymerization followed by ion exchange chromatography. This drug markedly differs from the other LMWHs in physiochemical characteristics and pharmacological profile.
>
> **Tinzaparin** (*Innohep*) is prepared by enzymatic digestion using *Flavobacterium Heparinicum* heparinase. This drug also contains large amounts of sodium bisulfate as an antioxidant.
>
> *Fareed et al. 1996:p.78*

Each depolymerization process results in structural changes to UH. Benzlation (enoxaparin) and heparinase digestion (tinzaparin) result in introduction of a double bond at the end grouping. Nitrous acid depolymerization (dalteparin) results in formation of anhydromannose (5 member ring).

> Chemical modifications of the end groups and internal structures, charge density, and degree of desulfination during manufacturing all add to the individuality displayed by the resulting products.[5p.79]

	Molecular weight
enoxaparin	4200 Daltons
dalteparin	6000 Daltons
tinzaparin	4500 Daltons

2.2 Mechanism of action

A recent review of LMWHs originating at McMaster University in Hamilton[7] summarizes what is seen as the main difference in mechanism of action between LMWH and UH:

> a) anti-thrombotic activity:
>
> Both UH and LMWHs exert their anticoagulant activity by activating antithrombin (previously known as antithrombin III). Their interaction with antithrombin is mediated by a unique pentasaccharide sequence that is randomly distributed along the heparin chains....
>
> Binding of the pentasaccharide to antithrombin causes a conformational change in antithrombin that accelerate its interaction with thrombin and activated factor X (factor Xa) and thrombin....
>
> In contrast, to inactivate thrombin, heparin must bind to both antithrombin and thrombin, forming a ternary complex. This complex can only be formed by pentasaccharide-containing heparin chains of at least 18 saccharide units. Whereas most of the chains of unfractionated heparin are at least 18 saccharide units long, fewer than half of those of LMWHs are of sufficient length to bind to both antithrombin and thrombin. Consequently, unlike unfractionated heparin, which has equivalent activity against factor Xa and thrombin, LMWHs have greater activity against factor Xa.
>
> *Weitz JI 1997:p.688*

The authors of the review also note other mechanisms of action. For example, they explain that both UH and LMWHs release tissue-factor-pathway inhibitor which inhibits factor Xa activity and ultimately thrombin formation.

2.3 Hemorrhagic effect

LMWHs causes less bleeding than UH. LMWHs bind less to platelets, do not increase micro vascular permeability, and cause less interference in the interaction between platelets and vessel walls.[6p.690]

2.4 Pharmacokinetics

The half life of LMWHs is two to four times that of UH: intravenous = 2 - 4 hrs; and subcutaneous = 3 - 6 hrs. LMWHs, in contrast to UH, bind less to plasma proteins, endothelial cells, and macrophages.[6p.690] As a result, LMWHs have more predictable anticoagulation effect and better bioavailability.

2.5 Standarization

Efforts to establish assays to determine bioequivalence have failed.[5p.87] In particular, anti-Xa methods have not allowed adjustment of LMWH potency. Anti-Xa is only one of many different biological properties of these agents. Tissue factor pathway inhibitor, for example, is recognized as an important contributor to the anti-thrombotic action of these agents.

3.0 Assessment of clinical research

3.1 Principles

1) Conclusive scientific evidence of problems related to substituting LMWHs could only be produced in one way: a well designed and properly conducted clinical trial comparing two or more LMWHs, for the same clinical indication. If one LMWH was shown to be superior to another in either efficacy or safety, then substitution should not occur.

2) Evidence of problems related to substitution, albeit indirect and inconclusive, could also derive from a collection of high quality clinical trials for the same clinical indication, each using a single LMWH. The LMWH could be compared to placebo, alternate anti-thrombotic drugs such as UH and warfarin, or mechanical devices (in the case of surgical prophylaxis). All trials would need full critical appraisal. If methodologically sound trials found one LMWH safer or more effective for a clinical indication than another, then the less effective LMWH would need, at minimum, additional clinical trial evidence vesus placebo to show that it is equivalent **before** substitution could be made. Ideally, the LMWHs in question should be compared in a single clinical trial.

3) Evidence of problems related to substitution cannot arise if only one LMWH has been studied for a clinical indication. Substitution, in this instance, would be based strictly on pharmaco-economics or policy principles.

4) Clinical trials of various agents, including LMWHs, for DVT prophylaxis and treatment have been too small to link specific therapies to final health outcomes such as clinically significant pulmonary embolism or death.

3.2 Methodology

3.2.1 Search strategy

The search was conducted from 1966 to 1997 using MEDLINE database and Current Contents. Key words used were DVT, LMWH, Dalteparin, enoxaparin, nadroparin, tinzaparin, thromboembolic disease and orthopedic procedures: knee and hip replacement surgery. To identify all systematic reviews on LMWH, the Cochrane Library was searched from 1993 to 1997. Subject headings used were "heparin, low molecular weight". Textwords were used to complement the search such as "heparin NEAR low NEAR molecular". Other clinical subjects headings were combined with the above search terms to ensure relevance: "thrombophlebitis" (MeSH), "thromboembolism" (tw), "dvt or deep NEAR venous NEAR thrombosis" (tw). Wherever possible the MeSH subject headings were "exploded" to maximize the scope of the search.

3.2.2 Inclusion/exclusion criteria

The principle search objective was for double-blind, randomized controlled clinical trials (RCTs) comparing two or more LMWHs for prophylaxis or treatment of thrombo-embolic disease.

Also included were RCTs comparing single LMWH with placebo, UH, and warfarin for prophylaxis and treatment of venous thrombo-embolic disease. Clinical trials involving single LMWHs for venous, as opposed to arterial, clinical indications were included because of their potential relevance to Pharmacare, that is, non-hospital patient care.

Excluded were trials with weaker study design or for clinical conditions treated exclusively within the hospital setting.

3.2.3 Search findings and critical appraisal results

1) Clinical trials comparing LMWHs

Clinical studies have **not** examined the relative efficacy and safety of LMWHs available in Canada, for any clinical indication, inside or outside hospitals.

The only published study directly comparing two LMWHs examined enoxaparin (benzylation, followed by alkaline hydrolysis, mw 4200) and reviparin (nitrous acid digestion, mw4653, **not available in Canada**) for the in-hospital prevention of DVT in 416 patients undergoing total hip replacement.[8] Both groups had similar efficacy, (venous thrombosis 9 and 10%, respectively) and rate of major bleeding (1% in each group).

2) Clinical trials using different LMWHs, but for the same clinical indication, potentially treated in the non-hospital setting

Several high quality trials were found involving single LMWHs for treatment of clinical indications of potential relevance to Pharmacare: non-hospital treatment of DVT and prophylaxis of hip and knee surgery.

Non-hospital treatment of venous thrombo-embolic disease
Non-hospital treatment of DVT is the first clinical indication for which LMWH reimbursement by Pharmacare is possible. Prior to non-hospital treatment of DVT, virtually all LMWH in BC was provided in and paid for by acute care hospitals.

In 1996, the TI conducted a systematic review and subjected the relevant trials to full critical appraisal. Two very similar, well designed and conducted, albeit open RCTs[9,10] compared LMWH administered primarily at home versus UH administered primarily in hospital for treatment of deep vein thrombosis (DVT). Each used a different LMWH, enoxaparin 1mg/kg bid (benzylation, followed by alkaline hydrolysis, mw 4200) and fraxiparin /kg dose (*Nadroparin*, nitrous acid depolymerization, mw4500). Results were very similar for efficacy (5.3% and 6.9% had symptomatic recurrent venous thrombosis, respectively) and safety (2% and 1% had major bleeds, respectively). These trials were rated as excellent, by the TI.

It seems reasonable to conclude, based on these similar, high quality clinical trials that enoxaparin and fraxiparin can be safely interchanged for the non-hospital treatment of DVT.

Prophylaxis of venous thrombo-embolic disease in patients undergoing total knee and hip replacement surgery
Venous-thrombo-embolic-disease prophylaxis in patients undergoing total knee replacement surgery could potentially become part of Pharmacare's jurisdiction in the future. Patients receiving total knee replacement (and perhaps hip replacement) may need LMWH prophylaxis subsequent to early hospital discharge.

In the instance of total knee replacement, two separate RCTs compare LMWHs (tinzaparin and enoxaparin, respectively) with a common comparator (warfarin) for prophylaxis of venous thrombo-embolism in patients undergoing total knee replacement.[11,12] Both studies found the LMWH more effective than warfarin and equally safe.

T = 45% and E = 37% versus W = 55% and 52% DVT, respectively
T = 3% and E = 2% major bleed versus W = 1% and 2%, respectively

Subsequent studies have compared enoxaparin, but not tinzaparin, to UH during total knee replacement. Conclusions regarding the validity of these trials and the interchangability of LMWHs for this clinical indication, will have to await full critical

appraisal. Full critical appraisal by the TI, in turn, will depend on local demand for non-hospital LMWH prophylaxis.

6.0 Conclusions

1) Despite the known pharmacological differences in LMWHs, no clinical outcome evidence has established a clinical significant advantage for one LMWH preparation over another for non-hospital clinical indications.

2) Clinical evidence in general, albeit scant, suggests that LMWHs are interchangeable. The one study[7] directly comparing LMWHs had similar results for both preparations for patients undergoing hip replacement. In the outpatient treatment of DVT (the one clinical indication in which trials were critically appraised) both preparations had the same efficacy and safety.

3) Indication by indication, systematic reviews and critical appraisals will be needed to determine the relative efficacy and safety of LMWHs. This level of critical analysis will be needed both for ideal studies that compare LMWHs directly to one another or the more common studies that continue to examine single LMWHs versus alternate drug therapy

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