Has the Time Come to Abandon Routine Use of Unfractionated Heparin in the Hospital Setting?

THE "PRO" SIDE

The first generation of iPhones represented a fundamental shift in communication, and follow-up versions quickly took on the functionality of "smartphones". But what happened to the old flip cell phones? Is anyone still using them? Just as mobile phone users shifted to smartphones, their service providers switched to new and improved practices, because supporting the old way of doing things became too costly. In health care, adaptation of new technology is inconsistent at best, and health care systems are often required to support a variety of platforms, simply because challenging prescriber preferences and engagement in change management is seen as too cumbersome. Much like the old flip phones, unfractionated heparin (UFH) continues to be used by some prescribers who "perceive" comfort, reliability, and cost-effectiveness with its use, but I will argue here that it's time to adopt newer therapies for treatment and prophylaxis of venous thromboembolism (VTE).

Isn't UFH old and cheap?

Well, UFH is certainly old, having been discovered in 1916 and undergoing its first clinical trails in 1935. UFH was originally manufactured from the mucosal tissues of slaughtered meat animals, such as porcine intestines and bovine lungs, with later advances in manufacturing occurring in the face of a contamination crisis. Recently, UFH manufacturing has undergone significant enhancements to ensure production according to the Current Good Manufacturing Practices of the US Food and Drug Administration, but this has resulted in substantially higher costs, with only a limited number of manufacturers now making this product.[1] Along with the increasing cost of UFH itself come various infrastructure costs that act as a drain on health care systems. For example, UFH infusions for VTE treatment require costly nursing time and monitoring by means of activated partial thromboplastin time (a test that is often inaccurate) or the increasingly expensive anti-Xa assay[2]; there are also costs associated with treating heparin-induced thrombocytopenia/thrombosis (HIT/T). The perceived cost-effectiveness of UFH has also been increasingly questioned. In this context, low-molecular-weight heparins (LMWHs) are seen as a safe, effective, and cost-effective alternative in the prevention and treatment of VTE.[3-5]

The LMWHs allow for home-based VTE therapy and prophylaxis with only limited monitoring requirements.[6,7] In a meta-analysis involving treatment of patients with VTE, there was no significant difference in risk between UFH and LMWH in terms of recurrent VTE (relative risk [RR] 0.85, 95% confidence interval [CI] 0.65–1.12), pulmonary embolism (RR 1.02, 95% CI 0.64–1.62), major bleeding (RR 0.63, 95% CI 0.37–1.05), and minor bleeding (RR 1.18, 95% CI 0.87–1.61).[6] Among medical patients, VTE prophylaxis with LMWH reduced the risk of VTE and deep vein thrombosis, with no increased risk of bleeding or death, relative to UFH.[7]

We know UFH is safe, so we should continue to use it, right?

Actually, UFH is associated with a higher risk of HIT/T relative to LMWHs.[5] At one Canadian site, introduction of a UFH-free HIT/T prevention policy dramatically reduced rates of HIT/T and resulted in significant system-wide savings. More specifically, following introduction of the policy, the annual rate of positive HIT/T assay results decreased by 63% and the rate of HIT/T decreased by 91%. Hospital HIT/T-related expenditures decreased by $266 938 per year in the avoid-heparin phase.[8,9] Broader implementation of UFH reduction by Alberta Health Services has also shown promising results, with investigators now finalizing results for publication.

Isn't there always a place for a good "burner phone"?

UFH does have a place in therapy, though only in very specific situations. For example, the use of UFH for coagulation management during cardiopulmonary bypass is likely to continue for some time to come, although the use of LMWH in this setting has been piloted.[10] The perception that UFH administration and its effects can be quickly stopped means there is continued reliance on UFH for planning surgical interventions that involve maintenance of anticoagulation. Greater understanding of the pharmacokinetics and pharmacodynamics of LMWHs will ultimately expand use of these agents, but for the time being UFH use is likely to continue.

Much like our embrace of the smartphone and the consequent demise of the flip phone, the time has come to say goodbye to

the use of UFH for mainstream VTE treatment and prophylaxis and to look to the LMWHs and the new oral agents (though granted, the latter is another topic altogether).

References

1. Oduah EI, Linhardt RJ, Sharfstein ST. Heparin: past, present, and future. *Pharmaceuticals (Basel).* 2016;9(3):38.
2. Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. *Pharmacotherapy*. 2012;32(6):546-58.
3. *Low molecular weight heparins versus unfractionated heparin for thromboprophylaxis in surgery, cancer and general medicine: a review of the cost-effectiveness and safety.* Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2013 Jul 2 [cited 2018 Aug 27]. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/jul-2013/RC0460%20LMWH%20vs%20UFH%20final.pdf
4. Klarenbach S, So H, Manns B, Tonelli M. *Economic evaluation of unfractionated heparin versus low-molecular-weight heparin to prevent venous thromboembolism in general medical and non-orthopedic surgical patients.* Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Apr [cited 2018 Aug 27]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK476597/
5. Junqueira D, Perini E, Penholati R, Carvalho M. Unfractionated heparin versus low molecular weight heparin for avoiding heparin-induced thrombocytopenia in postoperative patients. *Cochrane Database Syst Rev.* 2012;9:CD007557.
6. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med.* 2000;160(2):181-8.
7. Wells GA, Kelly S, Elliott J, Carrier M, Geerts W, Lee AYY, et al. Low molecular weight heparin and unfractionated heparin for the prevention of venous thromboembolic events in medical and non-orthopedic surgical patients: clinical review. Ottawa (ON): University of Ottawa Heart Institute; 2016 Dec [cited 2018 Nov 1]. Available from: https://www.ottawaheart.ca/document/low-molecular-weight-heparin-and-unfractionated-heparin-prevention-venous-thromboembolic
8. Nanwa N, Mittmann N, Knowles S, Bucci C, Selby R, Shear N, et al. The direct medical costs associated with suspected heparin-induced thrombocytopenia. *Pharmacoeconomics*. 2011;29(6):511-20.
9. McGowan KE, Makari J, Diamantouros A, Bucci C, Rempel P, Selby R, et al. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. *Blood.* 2016;127(16):1954-9.
10. Frederiksen JW. Cardiopulmonary bypass in humans: bypassing unfractionated heparin. *Ann Thoracic Surg*. 2000;70(4):1434-43.

Micheal Guirguis, BScPharm, PhD
Pharmacy Services, Kaye Edmonton Clinic
Alberta Health Services
Edmonton, Alberta

Competing interests: None declared.

THE "CON" SIDE

At times, old remains more functional than new, with the advantages of new being offset by certain shortcomings. For example, I still prefer reading a book or a newspaper over an electronic interface—both formats have their place, but I'm not ready to get rid of paper yet. Similarly, although the use of low-molecular-weight heparins (LMWHs) is expanding in Canadian hospitals, a role continues to exist for unfractionated heparin (UFH) in the prevention and treatment of venous thromboembolism (VTE).

Both UFH and LMWH have been studied extensively in the prevention and treatment of VTE, and both are recommended in current guidelines. More recently, the cost differential between UFH and LMWH has decreased, resulting in more frequent utilization of LMWH.

Which agent is selected for use in any given clinical scenario depends upon many factors, including efficacy, safety, and cost. In medical patients for whom thromboprophylaxis is required, the 2012 *Chest* guidelines recommend use of LMWH, low-dose UFH, or fondaparinux strategies, with the choice based on patient preference, compliance, ease of administration, and cost (grade 1B recommendation).[1] Among non-orthopedic surgical patients, the 2012 guidelines delineate the choice by risk of VTE but acknowledge that the risks of fatal pulmonary embolism, symptomatic VTE, and major bleeding are similar between LMWH and UFH.[2] For the acute treatment of deep vein thrombosis or pulmonary embolism in the absence of cancer, the updated 2016 *Chest* guidelines recommend long-term therapy with a direct oral anticoagulant (grade 2B recommendation) over vitamin K antagonists, and also suggest vitamin K antagonists over LMWH (grade 2C recommendation).[3] Little mention is made of initial parenteral anticoagulants in the 2016 report, but the 2012 guidelines recommended LMWH or fondaparinux (grade 1B recommendation) over UFH (grade 2C recommendation).[4]

Patients are diverse and at times are at extremes of weight or suffer from compromised end organ function. On the basis of current population trends, these demographic characteristics are expected to continue evolving. Although both LMWH and UFH can be used in most patients, LMWH may provide the advantages of fixed weight-based dosing and less laboratory assessment to ensure therapeutic levels. However, these advantages may actually serve as limitations in these subpopulations because of altered pharmacokinetics. For example, LMWH may accumulate in patients with impaired renal function, which increases the risk of major bleeding, resulting in the need for costly assessments of anti-Xa levels to examine the extent of anticoagulation. The Canadian product monographs for enoxaparin, dalteparin, and tinzaparin suggest that the safety and efficacy of these LMWHs have not been fully established for patients over 120 kg or below 45 kg.[5-7] The product monograph for enoxaparin suggests a dosage adjustment for patients with severe renal impairment (creatinine clearance < 30 mL/min), with a recommended dosage of 1 mg/kg once daily in this population.[5] The product monographs for dalteparin and tinzaparin provide no clear guidance for patients whose creatinine clearance is below 30 mL/min and suggest that risks for accumulation and bleeding exist; as such, individualized clinical and laboratory monitoring is recommended.[6,7] In the case of tinzaparin, further recommendations are provided for close monitoring of elderly patients with low body weight (e.g., < 45 kg) and those predisposed to decreased renal function.[7]

The ability to easily adjust UFH dosing with well-established laboratory tests and validated dosing nomograms may provide a critical advantage for UFH in patients with renal dysfunction and those at extremes of weight—populations commonly seen in Canadian hospitals. Data from cycle 1 of the Canadian Health Measures Survey (2007–2009) for the presence of chronic kidney disease indicated that the prevalence was 12.5% of the cohort studied, with 3.1% having stage 3–5 disease.[8] Acute kidney injury is common, representing 8%–16% of hospital admissions.[9] As common as renal dysfunction may be, attempting to dose LMWH at the extremes of body weight may become even more of an issue over time. According to Statistics Canada, 61.3% of adult Canadians were overweight or obese in 2015.[10] In Canada between 1985 and 2011, the prevalence of class II obesity (body mass index [BMI] 35.0–39.9) increased from 0.8% to 3.6%, and the prevalence of class III obesity (BMI ≥ 40) increased from 0.3% to 1.6%.[11] In the United States in 2014, the prevalence of morbid obesity (class III) was approximately 8% (or about 1 in every 12 people).[12] Limited data are available to guide dosing of LMWH in patients with morbid obesity, and dosing on the basis of total body weight may result in accumulation of these agents. Data for enoxaparin in this population suggests that a reduced weight-based dose (less than 1 mg/kg) is warranted and that full dosing may result in accumulation and increased risk of bleeding over time.[13,14]

In conclusion, the advantages of LMWH, which include ease of use and fixed dosing with minimal need for laboratory testing, may actually prove to be limitations in certain select populations that are seen clinically. Conversely, the acknowledged limitations of UFH may serve as advantages in these populations. As a result, UFH continues to play an important role in the management of patients who have or are at risk of VTE. Like your favourite book, older technology may at times be preferred to the new.

References

1. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl): e195S-e226S.
2. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e227S-e277S.
3. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease. Chest guideline and expert panel report. *Chest*. 2016;149(2):315-52.
4. Kearon C, Akl EA, Comerota A, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl): e419S-e496S.
5. [Pr]Lovenox® (enoxaparin sodium solution for injection, manufacturer's standard) [product monograph]. Laval (QC): Sanofi-Aventis Canada Inc; 2018 Sep 11 [cited 2018 Nov 18]. Available from: http://products.sanofi.ca/en/lovenox.pdf
6. [Pr]Fragmin® (dalteparin sodium) [product monograph]. Kirkland (QC): Pfizer Canada Inc; [revised 2017 Oct 10; cited 2018 Nov 18]. Available from: https://www.pfizer.ca/sites/g/files/g10037206/f/201711/FRAGMIN_PM_E_199798_10Oct2017.pdf
7. [Pr]innohep® (tinzaparin sodium) [product monograph]. Thornhill (ON): Leo Pharma Inc; [revised 2016 Feb 16; cited 2018 Nov 18]. Available from: http://www.leo-pharma.ca/Files/Filer/LEO_local_downloads/LEO-Pharma.ca/innohep%20PM%20(7.0)%20-%2023-MAR-2016.pdf
8. Arora P, Vasa P, Brenner D, Iglar K, McFarlane P, Morrison H, et al. Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. *CMAJ*. 2013;185(9):E417-23.
9. Sawhney S, Marks A, Fluck N, Levin A, Prescott G, Black C. Intermediate and long-term outcomes of survivors of acute kidney injury episodes: a large population-based cohort study. *Am J Kidney Dis*. 2017;69(1):18-28.
10. Vogel L. Overweight or overfat? Many Canadians are both. *CMAJ News*. 2017 Aug 31 [cited 2018 Nov 16]. Available from: https://cmajnews.com/2017/08/31/
11. Twells LK, Gregory M, Reddigan J, Midodzi WK. Current and predicted prevalence of obesity in Canada: a trend analysis. *CMAJ Open.* 2014;2(1): E18-26.
12. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016; 315(21):2284-91.
13. Lee YR, Vega JA, Duong HN, Ballew A. Monitoring enoxaparin with antifactor Xa levels in obese patients. *Pharmacotherapy*. 2015;35(11):1007-15.
14. Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. *J Thromb Thrombolysis.* 2015;39(4):516-21.

William M Semchuk, MSc, PharmD, FCSHP
Pharmacy
Saskatchewan Health Authority – Regina
Regina, Saskatchewan

Competing interests: None declared.