Brief Report

Assessment of the Stability of Dalteparin Sodium in Prepared Syringes for Up to Thirty Days: An In Vitro Study

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ABSTRACT

Background: If a low-molecular-weight heparin (LMWH) injectable formulation maintains its stability for up to 30 days, substantial cost reductions in hospital stay could be achieved with its use on an outpatient basis in patients who might otherwise be treated with IV heparin as inpatients.

Objective: This study was designed to assess the stability for up to 30 days of injectable solutions of the LMWH dalteparin sodium when repackaged in plastic syringes.

Methods: In the first part of the study, 1-mL and 3-mL plastic syringes were filled with the contents of a 10,000-IU/mL dalteparin ampule or a 25,000-IU/mL dalteparin multidose vial. In a separate part of the study, 1-mL and 3-mL syringes were filled with doses of 7500 IU and 10,000 IU, respectively, from a 10,000-IU/mL multidose vial. After the syringes were brought to room temperature or 4°C, the stability of dalteparin was assessed over 30 days by measuring anti-factor Xa levels.

Results: No significant loss of dalteparin activity was found for up to 30 days in the syringes after storage at room temperature or 4°C. The solutions retained anti-factor Xa activity at room temperature and under refrigeration.

Conclusion: Dalteparin is stable for up to 30 days when stored at room temperature or 4°C. The findings suggest that preparation of a postdischarge supply of dalteparin is feasible, contributing to more convenient and effective management of outpatients at risk for thrombotic complications. (*Clin Ther.* 2003;25:1219–1225)

Key words: low-molecular-weight heparin, anticoagulants, dalteparin, stability, deep-vein thrombosis, anti-factor Xa, storage, syringes.

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INTRODUCTION

Deep-vein thrombosis (DVT) is a complication of major surgery, particularly following orthopedic procedures. The postoperative risk period for DVT and pulmonary embolism can be managed effectively using prophylaxis with low-molecular-weight heparin (LMWH) (dalteparin or enoxaparin sodium) for 1 month following hip arthroplasty.[1] A search of MEDLINE was conducted to retrieve all articles relevant to evaluate the stability of LMWHs in circumstances similar to those described in this study. The literature search covered the period 1990 to the present and used the following search terms: *low-molecular-weight heparin, stability, dalteparin, enoxaparin, deep vein thrombosis, anti-factor Xa level, storage, multiple dose,* and *syringe.* A review of the literature showed that this therapeutic approach reduced the frequency of DVT significantly compared with conventional (7 to 14 days) prophylaxis.[1]

In the cost-containment environment of today's health care system, the management of acute DVT is rapidly shifting to the outpatient setting. Unfractionated heparin and warfarin were in use long before the introduction of LMWH as an antithrombotic alternative. Clinical studies[2,3] have demonstrated the outpatient management of DVT with LMWH to be safe, efficacious, and cost effective. The advantages of LMWH for outpatient use include ease of subcutaneous administration, predictable dose response allowing fixed-dose administration, no laboratory monitoring, and the convenience of once- or twice-daily dosing.[4–7] In the selection of literature to confirm the advantages of LMWH, the focus was on predictable dose response allowing fixed-dose administration, laboratory monitoring, and convenience of dosing.

Considering the proven advantages of LMWH prophylaxis in the outpatient setting, it may be more convenient and cost effective for the hospital pharmacist to prepare a postdischarge supply of repackaged syringes for patients to take home. Repackaging avoids patient handling and potential dosing errors and minimizes the risk of excessive needle sticks in the home setting.[8] Repackaging may decrease costs associated with medication preparation time by the pharmacist, particularly when LMWH is not stocked by the pharmacy. Ideally, doses of LMWH should be packaged for patient use and be stable for an extended period.

A supply of syringes with premeasured medication (to ensure accuracy) would be convenient and potentially improve patient compliance because patients otherwise would need to obtain syringes in limited number from a pharmacy every other day. For this approach to be feasible, maintenance of anticoagulant activity in repackaged plastic syringes for the duration of outpatient use must be demonstrated. The objective of this study was to assess the stability of the LMWH dalteparin sodium* as doses drawn from prepared multidose vessels (vials or ampules) into plastic syringes and stored for up to 30 days.

*Trademark: Fragmin® (Pharmacia & Upjohn Inc., Bridgewater, New Jersey).

METHODS

The first part of the study, conducted at the Massachusetts General Hospital clinical coagulation laboratory, assessed the stability of both dalteparin solution for injection (multidose vial) preserved with benzyl alcohol and dalteparin preservative-free solution for injection (ampule). Samples were aseptically drawn into 16 syringes by a laboratory technologist. Eight were 1-mL 27G × 1/2 tuberculin syringes (needle included, latex-free, Slip Tip; Becton, Dickinson and Co. [BD], Franklin Lakes, New Jersey). The other 8 were 3-mL syringes (latex-free, luer lock; Monoject, Sherwood Medical, St. Louis, Missouri). The needle used was a sterile BD 20G × 1/2 Precisionglide™ model. All testing was in duplicate and considered acceptable if optical densities were within 10% of each other. The test samples were processed the same way as routine patient samples.

The 1-mL and 3-mL syringes were filled with the contents of a 10,000-IU/mL dalteparin ampule or a 25,000-IU/mL dalteparin vial. The syringes were then stored at room temperature or 4°C. On days 0, 7, 14, and 30, 1 syringe from each container and storage temperature was selected. Fresh-pooled normal plasma then was spiked to a level of 0.5 IU/mL of LMWH from each syringe. To yield a final working concentration of 0.5 IU/mL in plasma, dalteparin was diluted in saline to obtain a 5-IU/mL solution, and this solution was then diluted 1:10 with pooled normal plasma.

The 0.5-IU/mL LMWH plasma standard was analyzed on an Amalung AMAX CS190 coagulometer (Sigma Diagnostics, St. Louis, Missouri) using a chromogenic anti-factor Xa heparin assay. The upper and lower limit anti-factor Xa control values were 1.22 U/mL to 1.48 U/mL (high control) and 0.66 U/mL to 0.90 U/mL (low control). With each run, high-control and low-control samples of LMWH were measured and found to be within acceptable limits. Testing was performed according to the manufacturer's specifications, and the coefficient of variation was <10%.

In a separate part of the study, the stability of dalteparin doses drawn from a 10,000-IU/mL multidose vial into plastic syringes and stored for up to 30 days was assessed. The 10,000-IU/mL multidose vial is produced only in the United States and is not available in Canada. Dalteparin 10,000-IU/mL solution for injection, preserved with benzyl alcohol, was aseptically drawn into 16 syringes. Of these, 8 were BD 1-mL 27Gx1/2 tuberculin syringes (needle included, latex-free, Slip Tip). The other 8 were Monoject 3-mL syringes (latex-free, luer lock); the needle used was a sterile BD 20Gx1/2 Precisionglide model. The needles were left on from the beginning of the study and capped tightly during storage (ie, the needles were never removed).

The 1-mL syringes were filled to 0.75 mL for a 7500-IU dose. The 3-mL syringes were filled to 1.0 mL for a 10,000-IU dose. All syringes were filled from a 10,000-IU/mL multidose vial. The syringes were then stored at 1 of 2 temperatures (room temperature or 4°C). On study days 0, 7, 14, and 30, 1 syringe for each dose and temperature was selected. Fresh pooled normal plasma was then spiked to a level of 0.5 IU/mL of dalteparin, using the LMWH from both the 1-mL and 3-mL sy-

ringes. To yield a final working concentration of 0.5 IU/mL in plasma, dalteparin was diluted 1:100 to yield a 100-IU/mL solution in saline, which was subsequently diluted 1:20 in saline to yield a 5-IU/mL solution. Finally, this solution was diluted 1:10 with pooled normal plasma. The 0.5-IU/mL plasma samples again were analyzed on an Amalung AMAX CS190 coagulometer using a chromogenic anti-factor Xa assay for LMWH. With each run, high-control and low-control samples of LMWH were shown to be within 2 SDs of the established control values.

Statistical Analysis

Statistical tests used to assess differences between syringes stored at different temperatures for different time periods were the analysis of variance and the Student *t* test. Significance was set at $P < 0.05$.

RESULTS

The results of the stability study for repackaging dalteparin 10,000-IU/mL solution for injection (ampule) and dalteparin 25,000-IU/mL solution for injection (multidose vial) into plastic syringes are shown in Tables I and II, which list the recovery values for the 2 preparations during the 30-day assessment. No significant loss of dalteparin activity was found for up to 30 days of storage at room temperature or 4°C. The stability of the preparation in the 10,000-IU/mL ampule was determined by comparing variations in anti-factor Xa levels. For the 1-mL syringe stored at room temperature, the initial anti-factor Xa value of 0.50 IU/mL essentially did not change, with a value of 0.49 at days 7 and 14 and a value of 0.50 at day 30. For the 3-mL syringe, the value was 0.48 at baseline and 0.50 on day 7, remaining at 0.50 for the rest of the study. The slight variations in values from 0.48 to 0.50 IU/mL were within the expected analytical precision of the assay, and none of the differences were statistically significant.

Comparable results were obtained for the syringes stored at 4°C. For the 1-mL syringes, the level of anti-factor Xa remained at 0.50 IU/mL from day 0 to day 14 and was 0.52 on day 30. Anti-factor Xa levels for the 3-mL syringes were 0.49 IU/mL initially and 0.50 at the other time points.

Insignificant variations in anti-factor Xa levels were also noted for the syringes filled with the dalteparin 25,000-IU/mL solution, whether they were stored at room temperature or 4°C. At room temperature, the 1-mL syringes had an anti-factor Xa level of 0.53 IU/mL at baseline, 0.54 at day 7, 0.55 at day 14, and 0.53 at day 30. This pattern of minimal variation was also similar for the other syringes assessed in the study.

The results of the stability assessment for repackaging dalteparin 10,000-IU/mL solution for injection (multidose vial; contents preserved with benzyl alcohol) into plastic syringes are shown in Table III. No significant loss of activity was found for up to 30 days. For the 1-mL syringes, the levels of anti-factor Xa at room temperature were 0.50 IU/mL at day 0, 0.57 at day 7, 0.56 at day 14, and 0.58 at day

Table I. Stability of dalteparin repackaged from a 10,000-IU/mL ampule (preservative-free) into plastic syringes and stored at room temperature (RT) and 4°C.

		Anti-factor Xa, IU/mL			
Syringe	Temperature	Day 0	Day 7	Day 14	Day 30
1 mL	RT	0.50	0.49	0.49	0.50
3 mL	RT	0.48	0.50	0.50	0.50
1 mL	4°C	0.50	0.50	0.50	0.52
3 mL	4°C	0.49	0.50	0.50	0.50

30. Values for the 3-mL syringes were 0.59 IU/mL at day 0, 0.52 at day 7, 0.60 at day 14, and 0.59 at day 30. The values obtained for syringes stored at 4°C also showed only minor variation. None of the differences were statistically significant.

DISCUSSION

On the basis of anti-factor Xa activity, dalteparin remains stable at room temperature (~22°C) and at refrigerated temperature (4°C) in syringes for up to 30 days when aseptic techniques are used. The maintenance of sterility is dependent on the technique of the person withdrawing dalteparin from its original vessel. The variation in recovery values can be attributed to the coefficient of variation in the assay and the minor variability associated with the preparation of dilutions. No conclusions can be drawn about the stability of dalteparin after 30 days, with syringes and needles of other manufacturers, or with lack of adherence to aseptic technique. Because LMWHs differ as a group with respect to their manufacturing process, their pharmacokinetic profiles, and their efficacy,[9] the stability demonstrated in this report for dalteparin may not apply to other commercially avail-

Table II. Stability of dalteparin repackaged from a 25,000-IU/mL multidose vial (preserved with benzyl alcohol) into plastic syringes and stored at room temperature (RT) and 4°C.

		Anti-factor Xa, IU/mL			
Syringe	Temperature	Day 0	Day 7	Day 14	Day 30
1 mL	RT	0.53	0.54	0.55	0.53
3 mL	RT	0.53	0.55	0.56	0.55
1 mL	4°C	0.53	0.51	0.51	0.51
3 mL	4°C	0.54	0.54	0.54	0.54

Table III. Stability of dalteparin repackaged from a 10,000-IU/mL multidose vial* (preserved with benzyl alcohol) into plastic syringes and stored at room temperature (RT) and 4°C.

		Anti-factor Xa, IU/mL			
Syringe	Temperature	Day 0	Day 7	Day 14	Day 30
1 mL	RT	0.50	0.57	0.56	0.58
3 mL	RT	0.59	0.52	0.60	0.59
1 mL	4°C	0.64	0.59	0.51	0.59
3 mL	4°C	0.65	0.60	0.55	0.60

*Available in the United States only.

able agents in this class. A small study assessing the use of dalteparin, enoxaparin, nadroparin, and tinzaparin drew each heparin into 5 plastic tuberculin syringes for each of the following time points: baseline; 1, 12, and 24 hours; and 2, 4, 6, 8, and 10 days.[10] The study found that 2 or more syringe needles of each LMWH showed blockage when stored at 22°C for up to 10 days when the needles were left attached. The study investigators concluded that blocked needles may prove to be a problem for patients under these dispensing and storage conditions.

Outpatient administration of LMWH is now a standard, universally accepted practice. Increased patient comfort and improved quality of life are also advantages when LMWH is used in the outpatient setting. According to quality-of-life assessment indicators, patients treated at home with LMWH have less impairment of physical activity and social function than those receiving unfractionated heparin in the hospital.[11] Patients have been shown to effectively perform self-injection and prefer to be treated at home.[12,13] In this study the needles were left attached and no blockage problems were encountered.

CONCLUSION

This report indicates that dalteparin is stable for up to 30 days when stored at room temperature or 4°C. The findings suggest that preparation of a post-discharge supply of dalteparin is feasible, contributing to more convenient and effective management of outpatients at risk for thrombotic complications.

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REFERENCES

1. Bergqvist D. The postdischarge risk of venous thromboembolism after hip replacement. The role of prolonged prophylaxis. *Drugs.* 1996;55(Suppl 7):5–59.
2. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med.* 1996;334:677–681.
3. Dedden P, Chang B, Nagel D. Pharmacy-managed program for home treatment of deep-vein thrombosis with enoxaparin. *Am J Health Syst Pharm.* 1997;54:1968–1972.
4. Martineau P, Tawil N. Low-molecular-weight heparins in the treatment of deep vein thrombosis. *Ann Pharmacother.* 1998;32:588–601.
5. Weitz JI. Low-molecular-weight heparins. *N Engl J Med.* 1997;337:688–698.
6. Chaffee BJ. Low-molecular-weight heparins for treatment of deep vein thrombosis. *Am J Health Syst Pharm.* 1997;54:1995–1999.
7. Siragusa S, Cosmi B, Piovella F, et al. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: Results of a meta-analysis. *Am J Med.* 1996;100:269–277.
8. Charland SL, Davis DD, Tillman DJ. Activity of enoxaparin sodium in tuberculin syringes for 10 days. *Am J Health Syst Pharm.* 1998;55:1296–1298.
9. Frydman A. Low-molecular-weight heparins: An overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. *Haemostasis.* 1996:26(Suppl 2):24–28.
10. Hamilton MA, Stang L, Etches-Wai S, et al. Stability of low molecular weight heparins (LMWH's) stored in plastic syringes. *Blood.* 2000;96:652a. Abstract.
11. Koopman MM, Prandoni P, Piovella F, et al, for the Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med.* 1996;334:682–687.
12. Wells PS, Kovacs MJ, Bormanis J, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: A comparison of patient self-injection with homecare injection. *Arch Intern Med.* 1998;158:1809–1812.
13. Harrison L, McGinnis J, Crowther M, et al. Assessment of outpatient treatment of deep-vein thrombosis with low molecular-weight heparin. *Arch Intern Med.* 1998;158:2001–2003.

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