

Fondaparinux: A Potential Alternative to Heparin for Long Term Anti-coagulation of Vascular Access Devices

Max Haid*

Medical Director, Sheboygan Acupuncture, LLC, Sheboygan, WI, USA

***Corresponding Author:** Max Haid, Medical Director, Sheboygan Acupuncture, LLC, Sheboygan, WI, USA.

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Abstract

Indwelling vascular access devices are in common use in modern medicine. Typically, these devices require flushing and anticoagulation with heparin between uses. Some of these patients ultimately develop heparin induced thrombocytopenia. Encountering just such a patient led the author to test fondaparinux in vitro as a long-term heparin alternative. The results, reported here, suggest that anticoagulation for vascular access devices lasting up to one year may be achievable using 0.1 ml of fondaparinux diluted with normal saline to a total volume of 3 ml. Doing so could preserve the vascular access devices of all patients as well as persons with heparin induced thrombocytopenia, reduce patient morbidity and significantly lower healthcare costs on a national scale.

Keywords: Vascular Access Device; HIT; Heparin Induced Thrombocytopenia; Fondaparinux; Flushing Solutions; Heparin Alternative

Introduction

The repeated use of heparin as a “locking agent” in VAD’s has been documented to produce unintentional systemic anticoagulation [1] as well as predispose patients to the development of HIT [2]. Many patients utilize VAD’s to facilitate antineoplastic treatment, long term antibiotic regimens and long term total parenteral nutrition to name the most common applications.

In-depth review of the literature produced a short list of non-heparin containing agents commercially available for the anticoagulation of VAD’s: argatroban, fondaparinux (FPX), refludan and sodium citrate. Their mechanisms of action and half-lives were reviewed and are presented in table 1.

Agent	Mechanism of action	Half-life (ref)
Argatroban	Inhibition of thrombin-catalyzed or induced reactions including fibrin formation	<20’ [3]
Fondaparinux	Anti-factor Xa	17-21 hrs. [4]
Lepirudin	A thrombin inhibitor found in the saliva of leeches; binds to thrombin preventing clot formation	21’ +/- 3’ [5]
Sodium citrate	Chelates ionized calcium (Clotting factor IV)	60’ +/- 2.9’ [6]

Table 1: Commercially available anticoagulants, their mechanisms of action and half lives are compared. Fondaparinux has a superior half- life measured in hours rather than minutes. The symbol ‘is used to denote minutes.

Systemic anticoagulation was deemed undesirable because of the risks of hemorrhage and lack of evidence that systemic anticoagulation would protect in-dwelling central venous or peripherally inserted central venous catheters from thrombosis. Based upon these considerations, the fact that it had already been approved for parenteral use and FPX's superior half-life, it was identified as the most appealing alternative to heparin for anticoagulation of vascular access devices.

Case Presentation

On a typical day in the Sheboygan, Wisconsin Vince Lombardi Cancer Clinic in 2011, this author encountered a patient with an indwelling vascular access device (VAD), variously referred to in the oncology vernacular as a "Port". The patient had been identified subsequent to its installation as having heparin induced thrombocytopenia or "HIT".

The Port was necessary to the patient's ongoing antineoplastic therapy. The standard of care required that, after usage, the VAD needed to be anti-coagulated to prevent it from thrombosing and becoming unavailable for further use. In addition to being upsetting to the patient, thrombosis of the Port results in the need for an additional invasive procedure, interruption of the treatment program, risk of venous embolism and cost.

In this particular patient, the presence of underlying HIT created a scenario in which use of heparin in any form, regular or low molecular weight, could result in serious harm or even death. An expedited review of the literature and discussion with the pharmacy staff did not offer any alternative anticoagulants. Per the pharmacy's recommendation, the patient's VAD was vigorously flushed and filled with saline not containing any anticoagulation. This experience prompted a search for a heparin alternative.

Materials and Methods

Study 1

The Food and Drug Administration approved package insert for FPX identifies the peak steady-state concentration to be 1.20-1.26 mcg/ml which results from a standard dose of 7.5 mg administered subcutaneously in a subject with a body mass of 50 - 100 kg. The typical retail cost for a package of two syringes each containing 7.5 mg of fondaparinux in May 2011, when these experiments began, was \$118 [7].

Two experiments were conceived to test fondaparinux. The method employed was the Lee-White clotting time [8] which was compatible with the author's absence of funding or a laboratory. Two syringes of the drug were graciously supplied by GlaxoSmithKline.

The first study was a dose seeking experiment comparing the package insert published peak plasma steady state concentration of 1.25 mcg/ml to 2.5 mcg/ml, 25 mcg/ml and saline control.

Two sterile plastic test tubes with caps were prepared each containing 0.1 ml of a more concentrated fondaparinux solutions (calculated to yield the final concentrations of 25 mcg/ml, 2.5 mcg/ml, 1.25 mcg/ml and saline) to which 2.4 ml of the author's whole blood were added and a timer started. It must be noted that the author was concurrently taking clopidogrel, 75 mg daily, 6 days a week and aspirin 81 mg Sundays, Mondays, Wednesdays and Fridays.

The tubes were maintained at room temperature and were tilted every 30' minutes until the first tube clotted then hourly x 4, then every 6 hours until the fifth day when the tubes were observed twice daily until the second and final tube clotted. The time from the venipuncture until the second tube clotted was recorded as the clotting time.

Results of Study 1

The 25 mcg/ml first tube clotted at 4 days, 22 hrs. The second tube had still not clotted when the experiment was terminated at 322 days. Thus, according to the paradigm of this study, the clotting time was in excess of 322 days.

The clotting time of the 2.5 mcg/ml tubes was 1 day, 34 minutes. The 1.25 mcg/ml tubes had a clotting time of 1 day, 34 minutes. The clotting time of the saline control was 42 minutes.

Materials and Methods

Study #2

The blood bank of Aurora St. Lukes Medical Center, directed by Dr. Kathleen Puca, provided a vial of ACD-A, an anti-coagulant solution they utilize, to allow comparison with Fondaparinux. Each 10 ml of ACD-A contains citric acid, anhydrous USP 73 mcg, Sodium Citrate, dihydrate USP 220 mcg, Dextrose Monohydrate USP 295 mcg and water for injection.

Five sterile plastic tubes with caps were prepared for each of three test groups: saline control; undiluted fondaparinux; and ACD-A. To each test tube, 0.1 ml of the corresponding test solution was added. Therefore, 0.1 ml of saline to the control; 0.1 ml of undiluted fondaparinux (containing 40.3 mcg of the active agent), and 0.1 ml of the ACD-A solution (containing 0.73 mcg of citric acid, 2.2 mcg of sodium citrate, 2.45 mcg of dextrose monohydrate) were added. Three ml of freshly drawn blood from the author were added to each tube. The tubes were maintained at room temperature. The first tube in each group was tilted every 20 minutes until it clotted. Then each successive tube within a given group was tilted at 20-minute intervals until the fifth tube clotted. The clotting time was determined to be the length of time from initiation of the experiment by introducing the drawn blood into the test tube until clotting of the 5th tube within each group. Once all the control tubes had clotted, the remaining tubes were checked three times per day for the first 8 days then just daily until terminated on day 369.

Results-Study 2

The saline control tubes had all clotted by 60 minutes of elapsed time. The ACD-A tubes had all clotted by day 12. The fondaparinux tubes had not clotted at all by day 369 at which point it seemed appropriate to terminate the study.

Discussion and Conclusion

The data reported here show a surprising duration of effect of fondaparinux in preventing clot formation *in vitro*. A VAD and its catheter are not topologically dissimilar from a tube. The VAD contains a chamber in its housing connected to the lumen of the its catheter which has an open end. What was observed in the artificial frame of reference presented here still needs to be confirmed in a clinical trial.

One commercially prepared 7.5 ml syringe of fondaparinux, whose retail cost is \$59, could produce 75 port-flushes, combined with 2.9 ml of saline. Even when factoring in nursing or pharmacist time to make these up, the costs are nominal. The material cost of each dose of the fondaparinux would be as low as 79 cents! It could be prepared locally by the medical, nursing or pharmacy staff.

The safety of subcutaneous administration of Fondaparinux (which is technically a parenteral usage) has already been established in the United States as evidenced by its approval by the Food and Drug administration. Therefore, its application as an anticoagulant for VAD devices would seem to be a low hurdle to clear.

This use of fondaparinux could apply to many different clinical settings including but not limited to: the emergency department, operating room, outpatient infusion center, home parenteral therapy, dialysis facility. In short, this agent could be a reasonable alternative to heparin in any setting where anticoagulation is needed.

A port-flush for maintenance of a VAD when the patient is not receiving treatment currently is billed out by the Vince Lombardi Clinic in Sheboygan, Wisconsin at a charge of \$240.87 [10]. For the five million VAD's installed in the United States annually, if one port-flush becomes clinically unnecessary due to the long term anticoagulation afforded by FPX, it would save the health care system \$1.2 billion! The mere substitution of FPX for heparin in persons receiving infusion chemotherapy monthly, assuming a mark-up from \$0.79 to, let's

say \$10.00 (to account for the 2 - 3 minutes it would take to make up a 3 ml syringe of FPX and saline) and the Aurora system's charge of \$60.87 for 100 units of heparin would save \$50.87 x 5 million VAD's = \$254 million per flush. This discovery presents an opportunity to help rein-in health care costs as well as to help those individuals with heparin induced thrombocytopenia.

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Conflicts of Interest

None.

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