Analysis of the Delivery of an Oral Heparin Formulation

By
Brenda Rogers
Kathy Eroschenko-Styer
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Background on DVT/PE

The body’s endogenous ability to halt the loss of blood from damaged vessels is known as hemostasis. This process is initiated when the sub-endothelium is exposed due to damage. Platelets adhere to this surface and begin to aggregate. The intrinsic and extrinsic pathways of the coagulation cascade begin. The end result of this process is the conversion of fibrinogen to fibrin, which helps to reinforce the platelet aggregate and allow for the vessels to be repaired. Once the tissue has healed, the body produces enzymes, which degrade the fibrin clot.

Thrombosis occurs when the fibrin clot occludes a blood vessel, causing the cessation of blood flow. In arterial blood vessels, the stasis of blood leads to a decreased transport of nutrients and oxygen to the tissues downstream. Thrombosis in the venous blood vessels prevents drainage and causes edema and irritation to the surrounding tissues. Furthermore, pulmonary embolisms can further complicate thrombosis of deep veins.

Heparin and other anti-coagulants, such as warfarin, are indicated in the treatment of and prophylaxis of thromboembolitic conditions, including deep venous thrombosis (DVT) and pulmonary embolisms (PE). Heparin is also used post-operatively in hip and knee replacements.

Heparin: An anticoagulant

Heparin is an endogenous mucopolysaccharide that was discovered by accident while looking at procoagulative compounds. The heparin used in drug formulations is derived from porcine intestinal mucosa or bovine lung. Two forms of heparin are currently available, unfractionated heparin or high molecular weight heparin (HMWH) which has a molecular weight of 5,000-30,000 Daltons and low molecular weight heparin (LMWH) which is characterized as having a molecular weight of <5,000 Daltons. While both are effective in the treatment of PE and DVT, LMWH has several advantages over the use of HMWH. These advantages include, subcutaneous administration once or twice daily, more predictable pharmacokinetics rendering stringent PTT monitoring not as critical, and less immunogenicity, which decreases the incidence and/or severity of the thrombocytopenia side effect. The therapeutic action of heparin is in its ability to bind the antithrombin III factor (ATIII) and augment its actions in inhibiting several coagulation factors. Both types of the heparin/ATIII complex affect Factor X (also known as the Stuart factor), but the HMWH/ATIII also inhibits the actions of Factor II. The inhibition of these coagulation factor(s) decreases the levels of thrombin, hindering the cascade of blood clotting which can be detected by measuring APTT values in the blood. Other clotting factors are also
affected, but are not responsible for the primary anticoagulative effects of heparin. Currently, anticoagulation therapy for DVT is treated by two main anticoagulation agents: LMWH (such as Lovenox®) and warfarin (Coumadin®). Heparin has a rapid onset, short half-life, low risk of teratogenicity, and relatively few drug-drug interactions rendering it pharmacologically superior over warfarin. However, warfarin is used for continuation of post-operative anticoagulation therapy due to the major drawback of heparin therapy: the necessity for administration via the injection route. Additionally, the switch from heparin to warfarin therapy takes 5-6 days due to the delayed onset and prolonged half-life of warfarin.

Approaches to Macromolecular Delivery

Historically, dosage forms of heparin and other macromolecules have been limited to the intravenous, intramuscular, and subcutaneous routes. Pain and discomfort from these routes cause non-compliance and inconvenience for the patient. Major barriers previously hindering the delivery of these compounds, via the oral route, have been their rapid enzymatic/metabolic degradation, biological and chemical instability, and limited absorption through the gastrointestinal epithelium.

To date, oral administration of heparin has not been successful due to its tendency to desulphate and undergo glycoside metabolism under the acidic conditions of the stomach. Also, due to its large size and negative charge, heparin absorption is very poor across the gastrointestinal tract. Approaches attempting to create stable dosage forms have included utilizing: pro-drugs, liposomes, permeability enhancers, co-administration of enzyme inhibitors, and polymer/enzyme inhibitors in conjunction with polypeptides. However, many of these approaches have had many drawbacks, which reduce their efficacy and usefulness. For instance, pro-drug administration would require synthesis of a new chemical entity that may not have the exact pharmacological properties needed. Liposomes are susceptible to degradation by bile salts and intestinal phospholipases that renders them ineffective. Temporary or permanent intestinal lining destruction can result with the use of permeability enhancers. Enzyme inhibitors display toxic side effects and their high production costs have decreased their popularity as delivery agents. Conjugate systems of polymers and enzymes also have low practicality due to their high production costs as well.

Despite the unsuccessfulness of previous endeavors, one company has attempted to formulate delivery systems for the administration of peptides and other macromolecules.
Emisphere Technologies, Inc. is a company in which their active area of research is in the development and formulation of novel delivery systems that allow oral administration of macromolecules. Their objectives for a new delivery agent have included the necessity to:

1) overcome degradation resulting from the acidic content and digestive enzymes of the gastrointestinal tract,
2) increase the absorption through cellular membranes,
3) minimize costs in the production of macromolecules, and
4) limit the variability in dosing \(^9\).

The solutions to each of these difficulties are discussed throughout the paper.

**Novel delivery system for oral heparin administration**

Sixty-eight compounds were evaluated for their ability to facilitate the oral absorption of heparin in rats. Some of these representative structures are given below.

![Figure 1](Oral delivery of Macromolecular Drugs 2000;169-186)

Out of the sixty-eight compounds, delivery agent 4 was chosen as the preclinical candidate and exhibited effectiveness in providing oral delivery in monkeys and humans. Synthesis of this compound is presented below.

![Figure 2](Oral delivery of Macromolecular Drugs 2000;169-186)
Agent 4 known as sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC) is an acetylated amino acid derivative \(^6\). The molecular weight is reported as 301 Daltons \(^3\). The specific selection of this particular compound was in part due to the number of methylene units between the acid and amide groups. When tested in vivo, compounds with 7, 8, or 9 methylene units were found to facilitate the greatest absorption of heparin. This was demonstrated through APTT values in monkeys \(^5\). Refer to figure 3.

![Figure 3](image-url)

Figure 3. Adapted from Journal of Medicinal Chemistry 1998; 41: 1163-1171.

Acquisitions of the 2 reactants employed in making SNAC were later modified. Due to considerations regarding cost and bulk availability of 8-aminocaprylic acid, a more cost efficient synthesis was needed. Therefore, in order to keep production costs low, different synthesis strategies were implemented to produce 8-aminocaprylic acid. Once a cost effective method was found, the carrier agent for heparin, SNAC, was produced.

The ability of SNAC to act as a carrier agent of heparin was determined by the utilization of several in vitro and in vivo trials. The results of one study in Cynomolgus monkeys showed that delivery of the SNAC:heparin combination increased APTT scores more than administration of heparin alone. Refer to figure 4 \(^10\).
The results of this and other trials supported SNAC’s use as a means of increasing the absorption of heparin via the oral route. The exact mechanism of how this carrier agent enhances heparin absorption is currently unknown and is being researched at this time. One hypothesis is that SNAC acts like a penetration enhancer such that it non-covalently interacts with the intestinal mucosal lining and enhances GI absorption. Earlier penetrations enhancers, as noted previously, caused epithelial damage at levels required for effective drug delivery. SNAC differs from other enhancement agents in that it does not appear to damage the intestinal tissues as evidenced by rat histological studies of the GI tract.  

A proposed mechanism of heparin delivery across the mucosal lining is illustrated in figure 6. In the first picture, the delivery agent is in green and heparin is shown in red. When they are in close proximity with each other such as in a solution, the delivery agent alters the physical characteristics of the heparin. The interaction between the two agents appears to be by weak intermolecular forces. Once the combination is orally ingested it moves to the GI tract. When in the GI tract, the complex comes in contact with intestinal membrane. The transport of heparin is due to the delivery agent. Without the agent, heparin would quickly be degraded and transport would not take place. In the third picture, the complex is acceptable for membrane transport and the delivery agent/heparin combination moves through the membrane. In the fourth picture you see the heparin separating from its delivery agent once it is across the membrane. Once inside, heparin can exert its pharmacological activity via the systemic circulation.
Efficacy Studies

The combination of SNAC:heparin has been compared to the intravenous and subcutaneous formulations of heparin to confirm its biological efficacy. One study compared the percentage of thrombus formations and mean thrombus weight between five treatments. Each treatment administered one of the following: 1) saline, 2) SNAC, 3) oral heparin without a delivery agent, 4) SNAC:heparin combination, or 5) IV heparin. A second phase of this study compared SNAC, oral heparin without a delivery agent, and SNAC:heparin and measured APTT.
scores. While the oral form was not proven superior to the alternative dosage form, it has shown to be as effective in the prevention of DVT in rat models. Refer to the figures 7 and 8.

Figure 7 and 8 Adapted from: The American Journal of Surgery 1998;176:176-178.

Similar conclusions have been made in studies comparing SNAC:heparin and subcutaneous administration.

**Pharmacokinetics/Physiochemical Properties**

Heparin is available as a sodium salt injectable. Following administration, immediate anti-coagulative effects are seen. There is a non-linear dose-dependent half-life that increases in intensity and duration with increasing doses. Half-life is estimated to be approximately 30-180 minutes; however, it is shorter in patients with DVT. Subcutaneous use delivers considerable individual variation in peak plasma levels with an average between 2-4 hours. Heparin is non-specifically and extensively protein bound ($V_d \approx 40-60\text{ml/kg}$). It is metabolized via the reticuloendothelial system and liver, with a possible secondary site in the kidneys. Renal excretion of both the unchanged and metabolized forms occurs rapidly due to the half-life.

Heparin sodium, USP is available as a powder and solution. The powder is white, amorphous and hygroscopic in nature. It is soluble in water (1:20) but is poorly soluble in alcohol. The aqueous solution of 1% is colorless to slightly yellow. Minor color variations do not affect efficacy. The solution should have a pH of 5-7.5, and can be sterilized using an autoclave. It should be stored at a controlled room temperature no greater than 40° C and should not frozen. Once prepared, the solution is stable for 24 hours at room temperature or in the refrigerator. Premixed bags after the seal is broken are stable for up to 4 days at room temperature or in the refrigerator.
Any variations of these parameters in the oral heparin formulation are unavailable at this time. Currently it is in Phase III clinical trials and specific data has not been published. Results of clinical trials have concluded a bioavailability of the SNAC:heparin complex to be 7.9% and 18.4% at 17.5 mg and 35mg of SNAC, respectively. It was concluded that when 25% propylene glycol (PG) was co-administered with SNAC:heparin, the bioavailability increased to 13.7% and 26.5% respectively. However, PG itself had no effect on the APTT levels. Therefore, it is probable that a small concentration of PG will be included in the final formulation. The presence of PG in the final preparation will allow for a lower dose of SNAC to be administered.

According to clinical trials, 15% of the administered dose of SNAC is found in the circulation and cleared renally. Other pharmacokinetic properties for SNAC have not been disclosed.

**Dosage and Administration**

Dosing of heparin is noted in the chart below. Heparin is never administered IM due to pain, irritation, and hematoma formation. Heparin can be given IV intermittently or continuously. Continuous IV infusion is preferable to other routes due to high incidence of bleeding. The standard diluent that heparin is administered in is 25,000-units/500 ml D₅W (premixed). In previous trials, the dosage used was 2.25g of the carrier agent SNAC and varying doses of heparin ranging from 30,000-150,000 IU. This was given in a drink that contained 30ml of the solution. Current trials indicate 15 ml of SNAC:heparin per dose every eight hours for thirty days for prevention of DVT in patients recovering from hip and knee replacement surgery. However, the exact amounts of the two agents were not stated.

<table>
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<tr>
<th>Heparin Dosage Guidelines</th>
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<tr>
<td>(Based on a 68 kg individual)</td>
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<tr>
<td><strong>Method of Administration</strong></td>
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<td>IV Infusion</td>
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Figure 9. Adapted from: Drug information handbook, 8th ed. 2000-2001.
Side Effects and Drug Interactions

It has been indicated that while heparin does have some side effects and drug interactions it is still preferred over warfarin. The main side effect due to heparin use is the complication of hemorrhage. Other complications that have been noted are: chills, fever, urticaria, hypersensitivity reactions, local irritation erythema, mild pain, hematoma, and ulceration. Thrombocytopenia has also occurred and can either be reversible or irreversible depending on patient variability. Rare occurrences of asthma, rhinitis, lacrimation, headache, nausea, vomiting and shock have been reported. Unfractionated heparin is pregnancy category C and low molecular weight heparin is pregnancy category B and can be used while breast-feeding. Interactions may occur with concurrent use of NSAIDS, certain antibiotics, nitroglycerin, digitalis, nicotine, antihistamines, and streptokinase. An extensive list of drugs with possible interactions can be found in the package insert for Lovenox®. Specific precautions are not yet indicated for the oral heparin formulation. SNAC appears non-toxic, but did cause nausea at high doses in humans. The specific dose at which nausea occurs was not stated.

Current Status of the oral SNAC:heparin dosage form

The liquid, oral heparin dosage form is currently in Phase III clinical trials. They began in December 1999 for prevention of DVT following total hip replacement surgery. The liquid formulation contains unfractionated heparin. The trial is a randomized three-arm study that is being carried out in the United States, Canada, and the United Kingdom. Approximately 3,000 patients in up to 95 centers are involved. Oral heparin at a dose of 15ml per dose every eight hours for 30 days is being compared to the injectable enoxaparin (Lovenox®) in the prevention of DVT following total hip replacement. However, there was no information given on the exact concentrations of the SNAC:heparin combination in the formulation. The primary efficacy endpoint is the occurrence of DVT during the treatment phase.

Future Dosage Forms

As of March 2000, a solid dosage formulation for unfractionated heparin entered Phase I clinical trials. A solid dosage form for LMWH is also in development. The carrier agent for this future family of products is that of SNAD (Sodium-N-amino decanoate). Using the new delivery agent SNAD, it has shown to increase the bioavailability of heparin to 38% relative to the subcutaneous injection. In addition the oral formulation has been well tolerated in primates.
studies conducted have shown SNAD to be four times more efficient than SNAC for oral heparin delivery. Many future uses for heparin such as in immune disorders and in cancer prevention are also under study at this time\textsuperscript{15}.

In conclusion, new delivery agents such as SNAC, hold a promising future in their use for the treatment and prevention of DVT. Non-compliance and inconvenience will be less of a problem and use outside of a hospital setting will lead to its popularity. Thanks to technological advances in the fields of pharmaceutics and medicinal chemistry have lead to overcoming the limitations in the delivery of polypeptides and other macromolecules. What once was thought impossible is now becoming feasible.
References:


15. Emisphere, Inc. Website. Available at: http://www.emisphere.com (cited 1/26/01)