Editorial

Porcine Mucosal Heparin Shortage Crisis! What Are the Options?

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Current dramatic developments concerning heparins and related drugs have been the focus of important discussions at several regulatory, clinical, and scientific levels. Unfractionated heparin is the most important of all the glycosaminoglycan drugs, without which, surgical and interventional procedures, hemodialysis, and surface coating of devices would not be possible. A better understanding of glycosaminoglycans has helped further their subsequent development. Heparin is the only anticoagulant with an effective antidote, protamine sulfate. Beyond heparin, related glycosaminoglycans such as sulodexide, hemoclar, and danaparoid are used for a variety of clinical indications. Sulodexide is a blended preparation containing low-molecular-weight heparin (LMWH) and dermatan sulfate as their main active components. Parenteral antithrombin agents such as argatroban and bivalrudin are used for anticoagulation but do not have a reliable antidote. Fondaparinux can be used parenterally but is devoid of any measurable anticoagulant effects in human blood.

Ever since its discovery more than 100 years ago, heparin and related drugs have been the focus of scientific and clinical investigations.1-3 Advances in technology has provided refinements for the production of heparin and related drugs. In addition, newer technologies including synthetic- and biotechnology-based approaches have also been used to produce heparin and related glycosaminoglycans. As polytherapeutic agents, these anticoagulants have other therapeutic properties as well. Low-molecular-weight heparins are derived from heparin and have been used for thrombotic and cardiovascular indications. The newer oral anticoagulant drugs have gradually replaced the heparins for the long-term management of thrombotic and cardiovascular disorders. However, these drugs have no impact on the use of heparin as an anticoagulant on critically important, and often life-saving, surgical and interventional procedures.

Heparin is sourced from the intestinal mucosa of animals, primarily from pigs. Other animals including cows and sheep can also be used for the manufacture of heparin. The 2008 heparin contaminant crisis resulted in a shortage of heparin supply due to regulatory withdrawals and has necessitated steps be taken at various levels to prevent potential future heparin shortages and develop alternate approaches. Imminent risk of a global shortage of heparin caused by the African swine fever afflicting the Chinese pig herd were predicted earlier by the Brazilian investigators.4 More recently, outbreaks of African swine fever in Europe (Belgium, Bulgaria, Hungary, Latvia, Moldova, Poland, Romania, Russia, and Ukraine) and Asia (China, Cambodia, North Korea, Laos, and Vietnam) have become a major concern. In China, it is estimated that 30% of the swine herd has already been lost and is expected to reach 50% by the end of 2019. This would represent a 25% reduction in the global pig population. The Bulgarian authorities have reported 30 outbreaks in over 10 regions, resulting in 130 000 pigs being slaughtered from a herd of 500 000. Such reductions in herd size will likely result in a shortage of porcine material which is used for the preparation of heparins and will eventually lead to a reduced production of porcine heparin necessitating alternate approaches for anticoagulation methods or alternative sources of heparin material. Concerns over the shortage of porcine heparin have been expressed globally and in particular in the United States where a majority of the heparin used is imported from China.5-7

To date, the US Food and Drug Administration (FDA) has not acknowledged the potential impact of the African swine fever outbreak on the heparin supply. Congressional leaders have raised concerns over the outbreak of African swine fever in China’s pig population and its impact on the supply of

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Chinese porcine heparin which represent almost 70% of this anticoagulant used in the United States.6 A letter signed by Chairman Frank Pallone, Jr. Democrat, New Jersey (D-NJ), Ranking Member Greg Walden Republican, Oregon (R-OR), Oversight and Investigations Chair Diana DeGette Democrat, Colorado (D-CO), Oversight and Investigations Ranking Member Brett Guthrie Republican, Kentucky (R-KY), Health Subcommittee Chairwoman Anna G. Eshoo Democrat, California (D-CA), and Health Subcommittee Ranking Member Michael C. Burgess, M.D. Republican, Texas (R-TX) expressed concern on the “U.S. dependence on Chinese heparin and on one animal source raises risks of shortages,” the bipartisan Committee leaders wrote in the letter. “Pharmaceutical researchers are raising concerns that the African swine fever outbreak in China ‘has the potential to cause an unprecedented shortage of heparin’s raw material.’”

While there is currently no overt evidence the pig shortage in China is impacting the current heparin supply in the United States, experience gained from past outbreaks indicate there is a 6- to 9-month lag time before a shortage would have effects on the United States heparin supply. The Committee leaders highlight the need to be prepared if this outbreak causes a shortage in the already-stressed US heparin supply. Alarmed by the potential heparin shortage, the hospital administrators and pharmacists have alerted clinicians regarding a conservative approach to use heparin and find alternated anticoagulants in the event of a crisis. Unfortunately, there are no firm recommendations identifying proper substitutes identifying heparin. Thus, some formal recommendations from professional associations and other health authorities are urgently needed.

As most of the US heparin supply is imported from China, the US government is concerned about the dependence on having one seemingly exclusive source for a product that could have dire health consequences if another domestic shortage were to occur. Open heart surgery, hemodialysis, and interventional procedures are totally dependent on unfractionated heparin. Moreover, the LMWHs used in the United States are mainly derived from porcine heparin. Other parenteral anticoagulants such as argatroban and bivalirudin can only be used in acute settings for short-term use with caution as they do not have any antidote.

Several studies have suggested that bovine and ovine heparins may be substituted for porcine heparin for anticoagulation purposes.8-10 As a matter of fact, bovine heparin was originally used for anticoagulant purposes until 2000. However because of the mad cow disease and other sporadic reports on adverse reactions, it was withdrawn from clinical use. Since then, advanced methods for the manufacture as well as eradication of biologic factors have provided safe and well-defined bovine heparins. Sheep heparin has also been clinically used in the past in some countries. Sheep heparin exhibits almost identical biologic profile as the porcine heparin. There is an adequate number of sheep to provide pharmaceutical quantities of heparin which can also be developed clinically as a substitute for heparin. It is concerning that despite its previous approval and clinical usage, bovine heparin is still going through a complicated review process by the FDA. Despite the similarities in both the biologic profile and chemical structure deeming sheep heparin to be bioequivalent to porcine heparin, the regulatory bodies consider it to be a new drug. At potency adjusted levels, both the bovine and sheep heparins behave in a similar fashion as anticoagulant and can be substituted for porcine heparin. As a contingency measure, the regulatory bodies should expedite the approval of bovine heparin or other alternative glycosaminoglycans by a fast-tracking regulatory process.

Substitution of porcine heparin with nonheparin drugs would not be easy. While the direct oral anticoagulant drugs such as apixaban and rivaroxaban have made a major impact on the long-term management of thrombotic and cardiovascular disorders, these drugs are of limited value for parenteral indications. None of these agents can be used for surgical or interventional procedures where heparin and related drugs are routinely used. Therefore, in the event of a shortage of heparin, these oral anticoagulant agents will be of limited value. Parenteral antithrombin agents such as argatroban or bivalrudin provide an option, however, there is no antidote available for the use of these antithrombin agents and the risk of hemorrhagic complications is disconcerting and compromises their benefit:risk ratio. Of the nonheparin glycosaminoglycan-related drugs, danaparoid, hemoclar (SP54), and sulodexide are currently available for clinical use. In comparison to sulodexide, danaparoid and hemoclar are relatively weaker anticoagulants when administered parenterally. Sulodexide is a drug which also has oral bioavailability and has shown to be clinically effective in the management of unprovoked deep vein thrombosis.11 It has a broader therapeutic index in comparison to oral anticoagulant drugs and may be useful in elderly and compromised patients. Sulodexide can also be used parenterally and exhibits a potency of 100 U/mg. In experimental studies, it behaves like heparin after parenteral administration. Moreover, it is also utilisable by protamine sulfate and other heparin neutralizing agents.12 Of the nonheparin glycosaminoglycans available, sulodexide may be a suitable option as a substitute for heparin in such indications as hemodialysis, interventional procedures, and as an anticoagulant for various purposes. While these indications are not approved for sulodexide use, the original pharmacodynamic data suggest that sulodexide can be used as an alternate to heparin in parenteral indications. Sulodexide can also be neutralized by protamine sulfate, and thus, may have potential to be developed for vascular and cardiovascular procedures.

Heparins and related glycosaminoglycans offer a wide array of parenteral anticoagulant/antithrombotic drugs for both the medical and surgical management of cardiovascular diseases. The anticoagulant and antithrombotic properties of heparins are also associated with anti-inflammatory and vasoprotective effects. Finding alternative sources for heparins through science and collaboration is urgently needed at this time, considering the current porcine heparin supply is threatened by the increased use of porcine mucosal tissue for the manufacture of LMWH and repeated outbreaks of diseases such as African
swine fever decreasing the global pig population. The development and regulatory approval of bovine and ovine heparin in the United States and the use of alternate glycosaminoglycans, such as sulodexide, offer practical approaches to offset the heparin shortage. As a blended glycosaminoglycan, sulodexide is a good candidate for further development as a parenteral anticoagulant that can be optimized for hemodialysis, interventional, and surgical indications. Both industry and regulatory agencies need to work together to develop plans to fast track review of these initiatives to avoid serious problems which may eventually result in compromised patient care.

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References
1. Fareed J, Hoppensteadt DA, Fareed D, et al. Survival of heparins, oral anticoagulants, and aspirin after the year 2010. *Semin Thromb Hemost.* 2008;34(1):58-73. doi:10.1055/s-2008-1066025.
2. Monakhova YB, Fareed J, Yao Y, Diehl BWK. Improving reliability of chemometric models for authentication of species origin of heparin by switching from 1D to 2D NMR experiments. *J Pharm Biomed Anal.* 2018;153:168-174.
3. Glass CA. Recombinant heparin—new opportunities. *Front Med.* 2018. doi:10.3389/fmed.2018.00341.
4. Vilanova E, Tovar AMF, Mourão PAS. Imminent risk of a global shortage of heparin caused by the African swine fever afflicting the Chinese pig herd. *J Thromb Hemost.* 2019;17(2):254-256.
5. Edney A. Mass pig deaths in China cause short supply of U.S. blood thinner. *Bloomberg.* August 30, 2019.
6. Bipartisan E&C leaders request FDA briefing on threat to U.S. heparin supply. Press Release. July 30, 2019. https://energycommerce.house.gov/newsroom/press-releases/bipartisan-ec-leaders-request-fda-briefing-on-threat-to-us-heparin-supply.
7. Toh M, He L. China has a new plan to solve its pork problem. *CNN Business.* July 26, 2019.
8. Jeske W, Kouta A, Farooqu A, et al. Bovine mucosal heparins are comparable to porcine mucosal heparin at USP potency adjusted levels. *Front Med.* 2019;5:360. doi:10.3389/fmed.2018.00360.
9. Fareed J, Bacher P, Jeske W. Advances in heparins and related research: an epilogue. *Molecules.* 2018;23(2):E390.
10. Hoppensteadt D, Maia P, Silva A, et al., Resourcing of heparin and low molecular weight heparins from bovine, ovine, and porcine origin. Studies to demonstrate the biosimilarities. *Blood.* 2015;126:4733.
11. Andreozzi GM, Bignamini AA, Davi G, et al., SURVET Study Investigators. Sulodexide for the prevention of recurrent venous thromboembolism: the Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: a multicenter, randomized, double-blind, placebo-controlled trial. *Circulation.* 2015;132(20):1891-1897.
12. Hoppensteadt D, Siddiqui F, Jeske W, Kouta A, Walenga JM, Fareed J. Relative neutralization of the anticoagulant, antiprotease and thrombin generation effects of sulodexide by a recombinant Xa decoy antidote (Andexxa). *Phlebol Rev.* 2019;41(suppl 1):41.