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# Can SARS-Cov-2 Infection Be GAGged? A Mini Review of Currently Available Potential Candidates Among the Heparin/Heparinoid Antithrombotics

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## INTRODUCTION

COVID-19 infection can vary from no symptoms, mainly in younger healthy subjects, to fatalities dying from viral or super-infection bacterial pneumonia, septic shock and multiple organ failure or cardiogenic shock. After entering the body, it then sets about disrupting the body's major defence mechanisms: the immune complement and haemostasis systems in gaining wider access to the vascular system and virtually all organs and tissues.

Normal cross-talk and interaction between these two systems can be life-saving in that it is designed to co-ordinate their ability to control and/or kill invading pathogens. However, the SARS-CoV-2 virus is able to disrupt the normal inflammatory response of cytokines and chemokines to combat the infection so that it becomes harmfully excessive. This induced hyperinflammatory response to the virus facilitates its invasion of the lung alveoli and gut mucosa and from there it sets about invading the vascular endothelial cells to gain access to the circulation. The resultant local endothelial cell damage attracts and activates platelets and leucocytes that release not only more cytokines but also many factors promoting thrombin generation and inhibition of thrombolysis. This procoagulant state leads to the development of a thrombotic (micro)angiopathy and local tissue hypoxia. Platelets also release high levels of PF4 (a cytokine) and PAI (an inhibitor of thrombolysis) into the circulation. Both are also able to inhibit the effects of APC, a natural inhibitor of thrombin production. Thus, virtually unopposed fibrin production ensues enhancing the risk of systemic thrombosis. PF4 also inhibits the interaction of Antithrombin (AT) and Heparin cofactor II (HCII) with the body's natural anticoagulant heparan sulphate (HS) and with administered antithrombotics that rely on these two natural inhibitors for their full anticoagulant activity. Unchecked the virus induced thrombotic angiopathy spreads to other tissues producing further hypoxic damage. Eventually haemostasis disruption can produce an intravascular coagulative disorder with hyperfibrinolysis and the possibility of bleeding, while circulatory disruption and hypoxia may lead to organ failure and death. Thrombin, APC, PAI and PF4 also interact with many cellular regulatory systems and with components of the complement system and the dysregulation by the virus coupled with the hyperinflammatory response contributes to the cellular and tissue damage that promotes viral invasion, spread, tissue destruction, and replication.

Since haemostatic disruption and thrombosis are key factors in the pathogenesis of COVID-19 infection then anticoagulation would appear to be important for its management. However, the disruption of the cooperation between the haemostatic and immune-systems for optimal protection of the body by the virus has turned our attention to the heparins and heparinoids that appear to act independently on both systems.

### Glycosaminoglycans (GAGs), Haemostasis and the Immune System

Heparins and heparinoids are members of a ubiquitous family of heterogeneous mixtures of linear, sulphated glycosaminoglycans (GAGs). They consist of covalently linked hexoses with side-chain differences that largely determine the type of GAG, i.e., heparin sulphate (HP), heparan sulphate (HS) or dermatan sulphate (DS). They are most commonly found as protein complexes (proteoglycans) on or embedded in the surface of cells and in the glycocalyx and basement membranes. Only HP is found intracellularly in mast cells. Their function is determined by their size and shape which in turn is dependent on chain length, order of hexoses along the chains, the different types of hexose

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present, the side-chain substitutions that determine their general protein binding ability and whether or not they possess a variety of short sequences that allow binding to a specific protein. This macro and micro-chemical heterogeneity is largely tissue-site specific.

Some of the HS chains possess antithrombotic actions (i.e., equivalent to commercial unfractionated heparin) because they include specific hexose sequences that bind to and catalyse the actions of the body's natural clotting inhibitors Antithrombin (AT) and Heparin Cofactor II (HCII) and other haemostasis controlling proteins. In addition, the chemical structure of the GAGs also determines their ability to influence the cross-talk between haemostasis and the immune system both dependently and independently of their interaction with clotting cascade proteins. As a result, they also participate in various physiological processes from regulation of angiogenesis to the sieving function for proteins of the glycocalyx, from helping to control cell and vascular permeability to cell-cell interactions. These activities underlie the importance of GAGs in homeostatic maintenance. Thus, commercially available GAGs derived from natural GAGs (unfractionated heparin (UFH), low molecular weight heparins (LMWHs), sulodexide and danaparoid sodium are of interest in many disorders where there is disruption of both haemostatic and immune systems, e.g., heparin-induced thrombocytopenia, sepsis and antiphospholipid syndrome.

**Commercial GAG antithrombotics**

UFH and the LMWHs consist of HP with traces of DS and chondroitin sulphate, sulodexide contains 80% HP and 20% DS and danaparoid is about 85% HS with about 12% DS and a small amount of chondroitin sulphates. The HS in danaparoid differs from the endogenous HS anticoagulant in having a lower molecular weight average and smaller chain length with less overall negative charge density. The HS in danaparoid also includes only a small (5% by weight) sub-fraction whose chains contain the specific pentasaccharide that allows binding to AT compared with about 30% of the UFH chains and 20% of the LMWH and sulodexide chains. However, the remaining 95% of the HS subfraction of danaparoid also contributes to its antithrombotic activity by directly inhibiting thrombin mediated Factor IX activation, an important positive feedback loop in states of high thrombin generation.

The average chain length and structure determines their interaction with AT and HCII and hence the specificity and strength of interaction with various clotting cascade proteins. Their main effects overall are inhibition of thrombin generation and its activity but the ratios of these activities vary considerably. Nevertheless, their overall antithrombotic activities are very similar. However, their differences in structural and physio-chemical characteristics provide differential effects on bleeding induction, interactions with other haemostasis systems (e.g., thrombolysis) and their ability to influence immune reactions. Subtle differences in shape and charge distribution of the GAG chains influences their interactions. Hence while the mostly animal or tissue experimental data with the isolated antithrombotics may not precisely reflect the actions of the natural product from which they were derived in-vivo (particularly since the experimental conditions, i.e., animals, tissues and reagents used are an often-unnatural mix) the possibility that some of the results may translate into a useful therapeutic effect is intriguing.

**Is there a preferred candidate for testing in a clinical trial?**

Heparin and the LMWHs have already been used mostly for thrombosis prophylaxis with success in COVID-19. However, many of their in-vitro/ex-vivo immune-modulatory actions occur optimally at therapeutic dosing levels. If this is the case then in the more severe stage of COVID-19 the heparins may further increase the bleeding risk in the presence of thrombocytopenia and a DIC-like syndrome with increased fibrinolysis. In addition, heparin resistance may occur due to the high PF4 and other cytokine levels and the development of various types of immune heparin-induced thrombocytopenia (HIT) is also possible. This leaves sulodexide and danaparoid both of which have been shown to be effective antithrombotics with a low bleeding potential even at therapeutic dosing levels. Both products have shown immune-modulatory activity in many model systems, can reverse angiopathy and can restore the integrity of the glomerular basement membrane to prevent protein loss into the urine in diabetics. There are some similarities and differences in their actions on immune responses but unfortunately there are no direct comparisons either clinically or in experimental models. The advantages of danaparoid are its inability to form the necessary ultra-large complexes with PF4 required for the induction of the anti-platelet HIT antibody, its smaller reliance on AT levels, its ability to preserve antithrombotic APC levels that may be important for inhibiting PAI activity and its safety at therapeutic doses. Furthermore, danaparoid has been successfully used to treat disseminated intravascular coagulation including a hyper-fibrinolytic variant and can be safely administered to patients with either renal or hepatic failure, to children and pregnant women.

However, it may not be just a question of which is the best candidate for investigation in COVID-2 infection but at which stage might any of the GAG antithrombotics be most useful (if at all). At different stages of the disease or for certain at-risk patients it is possible that the balance between disturbances of inflammatory/immune factors and vascular/haemostatic factors favours the use of one GAG antithrombotic over the others. Furthermore, the ability of the SARS-CoV-2 virus to mutate rapidly challenges the efficacy of the responses of both the body's natural defence mechanisms and the vaccines developed against it but is less

likely to diminish beneficial effects (if any) of the heparins and heparinoids.

## CONCLUSION

The SARS-CoV-2 virus has taken the world by surprise not only because of its severity in the face of modern hospitals, techniques, medicines and trained staff, but also because of its effects on the most vulnerable countries and members of society. This emphasises the need for more generally affordable drugs to combat the disease. GAG antithrombotics have been with us for decades because of their efficacy and safety, when used according to the manufacturer's recommendations, and their relatively low cost. In particular, the products that appear to combine antithrombotic activity with independent immune-modulatory activity and possess the best safety profile at the required therapeutic doses, i.e., danaparoid and sulodexide, merit consideration in the management of SARS-CoV-2 infection, but only suitably designed, sufficiently powered clinical trials, can provide an answer.

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