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Mini-Review

A Mini Review: A Rationale for the Possible Role of Heparin/Heparinoid Antithrombotics in the Management of COVID-19 Infection

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ABSTRACT

COVID-19 infection can vary from no symptoms in mainly younger healthy subjects to fatalities dying from viral or super-infection bacterial pneumonia, septic shock and multiple organ failure or cardiogenic shock mainly in older subjects. The virus is inhaled and invades the cells of the mouth, upper and lower respiratory tracts by high-jacking cell surface ACE-2 receptors and the transmembrane protein Neuropilin-1 to enter cells. It then sets about disrupting the responses of the body's major defence mechanisms: the immune complement and haemostasis systems, to gain access to the vascular system and virtually all organs and tissues.

Keywords: COVID-19; Inflammatory factors; Immune modulatory

INTRODUCTION

Normally these two systems engage in cross-talk and interaction that co-ordinate their ability to control and/or kill invading pathogens. However, the response to SARS-CoV-2 virus invasion quickly leads to dysregulation of both systems so that the reactions of the innate immune system, release of cytokines and chemokines and the haemostasis adjustments to limit viral spread and combat the infection become harmfully excessive [1]. This initially local hyper inflammatory response causes cell disruption and death thus facilitating viral invasion of the lung alveoli and gut mucosa cells, from where it accesses the vascular endothelium. Here it disrupts cell adhesion causing fluid leakage into the alveoli and tissues and invades and disrupts the function of the endothelial cells. This endotheliitis causes a further outpouring of inflammatory agents and clot promoting factors (PF4, Tissue Factor, v Willebrand's Factor etc.). Platelets and leucocytes attracted to the scene become activated to release more inflammatory and pro-coagulant factors including PAI that inhibits formation of thrombolytic plasmin and the action of APC, one of the body's natural inhibitors of thrombin production. The combination of accelerated thrombin generation, thrombolysis inhibition and endothelial damage produce a thrombotic (micro) angiopathy with local tissue hypoxia that further augments the expression of pro-inflammatory and pro-coagulant signals [2]. The continuing dysregulation of the normal interactions of thrombin, APC, PAI and PF4 with many cellular regulatory systems and with components of the complement system, coupled with the hyper inflammatory response amplifies the cellular and tissue damage to promote viral invasiveness, replication, spread and tissue destruction [3].

The body's natural 'anticoagulant' is not heparin but a Heparan Sulphate (HS) that acts by accelerating the inhibitory activity of Antithrombin (AT) on thrombin generation and activity. Another natural inhibitor of the clotting cascade is Dermatan Sulphate (DS) that accelerates Heparin Cofactor II (HCII) inhibition of thrombin activity. Under normal circumstances APC, AT, HCII and the HS anticoagulant are important controls of the clotting cascade. High levels of PF4 however, bind HS and DS thus preventing their anticoagulant activity [4]. In addition, increased expression of heparanase in the tissues of COVID-19 patients also inactivates the HS anticoagulant and contributes to the pro-coagulant state. In some patients the haemostatic disruption develops further into an intravascular coagulative disorder with hyperfibrinolysis and the possibility of bleeding, circulatory failure, organ failure and death [5,6]. Meanwhile the virus has gained access to the circulation and once there all organs and tissues appear to be at risk of invasion especially if local hypoxia and previous damage are present. Especially the elderly, the obese, diabetics, hypertensives and those with serious vascular disease or immune deficiency or autoimmune disease have a high risk for serious outcomes of

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COVID-19 infection because they already have one or more of the preceding abnormalities that facilitate viral invasion and replication [7].

GAGS AS POTENTIAL TREATMENT

The current SARS-CoV-2 pandemic has seen the introduction of many old and new drugs to reduce viral numbers and limit the damage it causes. Since haemostatic disruption and thrombosis are key factors in the pathogenesis of COVID-19 infection then antithrombotics would also appear to be important for its management. Furthermore, the ability of the virus to disrupt the co-operation between the haemostatic and immune-systems has turned attention to antithrombotics that appear to act on both systems. The heparins and some heparinoids (linear sulphated Glycosaminoglycans (GAGs)) have demonstrated immune modulatory activities that appear to be independent of their antithrombotic activity and treatment with a heparin is associated with improved clinical outcomes in COVID-19 patients. However, there have been no comparative studies to elucidate the optimal anticoagulant to use, the best time to initiate treatment and the optimal dosing intensity required [8].

The GAG antithrombotics can be classified into 2 main groups – the Heparin/Heparan Sulphates (HP/HS) and the Dermatan/Chondroitin Sulphates (DS/CS) distinguished by the presence of glucosaminoglycans and galactosaminoglycans respectively. GAGs occur everywhere in the body mainly protein bound as proteoglycans on and within cell membranes or in cellular basement membranes and the glycocalyx protecting the luminal surface of endothelial cells [9]. Only HP is found intracellularly in mast cells. HP and HS are loosely differentiated by their higher content of iduronic acid or glucuronic acid respectively. The pattern of repeating disaccharide unit in GAGs, chain length and order of units along the chain, acidity of their hexose side-chains and the presence of a specific short hexose sequences combine to determine their animal and tissue specificity, their specific binding to many proteins and their participation in many physiological activities, e.g. angiogenesis regulation, vascular permeability to plasma and proteins, cell-cell interactions, cancer spread, lipoprotein processing, antithrombotic activity etc [10].

The GAGs currently available as approved antithrombotics are extracted and purified from animal tissues by chemical and physical means. Hence some structural modification during isolation is likely. Purified Unfractionated Heparin (UFH) is also split chemically or enzymatically into shorter GAG chains to provide the Low Molecular Weight Heparins (LMWHs) that were originally developed to reduce the parent heparin's platelet binding and hence the bleeding risk. The final (tightly regulated) composition of each GAG antithrombotic provides either an almost single or a mix of GAG groups, e.g. heparin and the LMWHs consist of HP with traces of DS and CS sulphates, sulodexide contains 80% HP and 20% DS and danaparoid is about 85% HS with about 12% DS and a small amount of CSs. All these antithrombotics are heterogeneous with regard to chain length and the degree of sulphation and acidity that determines the intensity of their overall negative charge density [11]. HS is the endogenous equivalent of UFH since endogenous HP does not primarily appear to function as an anticoagulant. However, the GAG chains of the HS in danaparoid differ from those of the endogenous HS anticoagulant in being much shorter (with a lower Molecular Weight average (MWave)), having a lower overall negative charge density and having far fewer chains that include the specific pentasaccharide binding site for AT [12]. About 30% of heparin chains, 20% of the LMWH and sulodexide chains contain this sequence but only 4% of the danaparoid HS chains. The differences in overall negative charge density: heparin>LMWH>sulodexide>danaparoid and chain length also determine their ability to bind to circulating proteins. Thus UFH is highly bound while danaparoid only binds its target proteins (AT, HCII and FIX). Chain length also gives specificity to the binding and activation of AT which is strongest for heparin (MWave 15 kD) and the LMWHs (MWave 4-7 kD), weaker for sulodexide (heparin fraction MWave 7 kD) and weakest for danaparoid (MWave 5.5 kD). The DS content of sulodexide (MWave 25 kD) has a greater inhibitory action on thrombin activity than that of danaparoid (MWave 5.5 kD). Danaparoid also directly inhibits thrombin mediated Factor IX activation, an important positive feedback loop in states of high thrombin generation so that the overall effects UFH, LMWHs, sulodexide and danaparoid on thrombin generation and thrombus inhibition are very similar despite the different physiological mechanisms involved.

However, the macro- and microheterogeneity of the various GAG products produces different effects on bleeding (heparin>LMWH>sulodexide>danaparoid) and their ability to influence immune reactions, some of which appear to be independent of their antithrombotic actions [13]. Many effects on the immune system are related not only to chain length, degree of sulphation and type and position of the hexoses but also to specific chemical structures within them, e.g. the presence or absence of 6-O, 3-O or 2-O sulphate groups and N-sulphation or N-desulphation etc., that subtly affect the shape of the GAG molecules, their binding properties and hence the specificity of the immune interactions. Despite their animal and tissue specificity, the GAG antithrombotics, despite possible modifications during their isolation and purification, have shown various immune-related actions in animal model and isolated tissue and cell experiments that underlie their importance in homeostasis. These include control of glycocalyx/basement membrane permeability, tumour cell growth and metastasis, cell proliferation, angiogenesis, anti-inflammatory activity, reperfusion injury and endotoxin induced injury. Some of these actions have been demonstrable in volunteer and patient studies. Thus the possibility that these results may translate into a useful therapeutic effect in patients with COVID-19 infection is intriguing.

DANAPAROID AND SULODEXIDE

Is there a preferred candidate for testing in a clinical trial? Heparin and the LMWHs have already been successfully used in COVID-19 infection mostly for thrombosis prophylaxis. However, many of their *in-vitro/ex-vivo* immune-modulatory

actions occur optimally at therapeutic dosing levels which could increase the risk of bleeding, especially in the more severe stage of COVID-19 infection. In addition, heparin resistance may occur due to the high PF4 levels with the possible development of immune Heparin-Induced Thrombocytopenia (HIT). Sulodexide and danaparoid are effective antithrombotics with a low bleeding potential even at therapeutic dosing levels [14,15]. Both products have shown immune-modulatory activity in many model systems and both can reverse urinary protein loss in diabetics by restoring the integrity of the glomerular basement membrane. However they have not been directly compared either clinically or in experimental models [16]. Additional 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 ability to preserve antithrombotic APC levels that may be important for inhibiting PAI activity and preventing rebound thrombosis and its continued antithrombotic efficacy at moderate to low AT concentrations. Furthermore, danaparoid has been successfully used to treat heparin-induced thrombocytopenia, in which it interferes with the interactions of the HIT antibody with UFH and platelets, and in disseminated intravascular coagulation, including a hyperfibrinolytic variant, and can be safely administered to patients with renal or hepatic failure, to children and pregnant women.

Recent publications have shown that in addition to standard treatment sulodexide in a prospective trial v placebo reduced oxygen requirements and hospital stay in COVID-19 patients. Similarly case reports of danaparoid use in patients with thrombocytopenia and thrombosis associated with severe COVID-19 and with an anti-SARS-CoV-2 vaccine have also shown it to be useful. Nevertheless, 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 [17].

CONCLUSION

The ability of the SARS-CoV-2 virus to mutate rapidly challenges the responses of both the body's natural defence mechanisms and the efficacy of vaccines developed against it but it is possible that the efficacy of the GAG antithrombotics is less likely to be influenced by the emergence of new variants. The advantage the virus takes of poverty and over-crowding, political dithering over costs, increase the need for cheaper drugs to prevent or reverse its action. Furthermore, the possibility that more dangerous variants of the virus will arise increases the need for effective drugs that do not specifically target the virus itself.

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 effects of) COVID-19 and vaccine-induced thrombosis. Both danaparoid and sulodexide have been with us for decades because of their efficacy and safety when used according to the manufacturer's recommendations. They appear to combine antithrombotic activity with independent immune-modulatory activity and possess the best safety profile at the required therapeutic doses. Thus they merit consideration in the management of SARS-CoV-2 infection, but only suitably designed, sufficiently powered clinical trials, can provide an answer to the questions of which is the most suitable, in which type of patient and at which stage of the disease.

CONFLICT OF INTEREST

The author led the clinical development of danaparoid sodium until his retirement in 1999 and has since worked as an independent clinical consultant with an interest in anticoagulants.

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