Argatroban immobilization on Cu-modified PVC and PU

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Abstract

Thrombosis induced by biomaterials after their contact with blood is a main reason of medical device failure. To make material surface more thromboresistant different approaches have been undertaken. NO generating biomaterial has proven to play a crucial role in the prevention of thrombosis by inhibiting the platelets activation/adhesion. However, immobilization of the direct thrombin inhibitors onto material surface makes material more thromboresistant by preventing thrombin-mediated blood clotting. The aim of this research was to immobilize argatroban a direct thrombin inhibitor with reliable and predictable anticoagulant effect onto PVC and PU polymers. Both polymers were first imprinted with Cu ions for the catalytic generation of NO (this research was reported earlier). Argatroban was immobilized on the Cu-modified PVC and PU using the polydopamine ad-layer via the Michael addition/Schiff base reaction. The amount of argatroban bound to the polymer surface was measured (spectrophotometric determination at 334 nm) as 11.92 nmol/cm2 on PVC and 13.10 nmol/ cm2 on PU surface.

Keywords: blood clotting, Cu-modified, immobilization.

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Introduction

Assay using thrombin-specific chromogenic substrate was performed to evaluate the thrombin inhibition capacity of argatroban-modified polymers. It was found that both Argatroban-modified polymers inhibit thrombin activity in PBS. In order to confirm the NO generation catalyzed by Cu/Arg-modified PVC and PU samples after incubation with 100 ?M GSNO/GSH in the PBS during 1h was examined using ArrowSTRAIGHT??? nitric oxide measurement system (Lazar Research Laboratories, Los Angeles, CA, USA). The Cu/Arg-modified PVC and PU generate NO with the rate 1.27-1.66??1010 mole/cm2???min which is within the physiological level. From the data obtained it???s possible to conclude, that immobilization of Argatroban to the Cu-modified polymers showed combine abilities: i) generate NO caused by Cu ions and ii) have capacity to inhibit thrombin formed in the blood via surface immobilized argatroban.

The potential of thrombus development is still a major drawback of existing extracorporeal circulatory life support (ECLS) technologies. Extracorporeal devices are now used in clinical practise with systemic anticoagulation to avoid clot formation within the circuit. Patients on systemic anticoagulation, on the other hand, are at a significant risk of bleeding, which can be life-threatening. Despite substantial research into developing extracorporeal circuits with nonthrombogenic surface qualities, clinical success has been mixed, and their application has been restricted to certain clinical circumstances. 1–8. A biomaterial that is analogous to vascular endothelium is appropriate for extracorporeal circulatory devices. A surface that contains both a thrombin inhibitor and a nitric oxide-releasing substance is especially intriguing since these agents target fibrin production and platelet activation, which are both involved in the development of thrombus. A biomaterial that contains antithrombin and antiplatelet characteristics has a better safety profile than systemic anticoagulation because it delivers localised anticoagulant action, which eliminates the danger of bleeding that systemic anticoagulation entails. Unfractionated heparin is the most often used systemic anticoagulant for extracorporeal circulatory life support (ECLS)9–11. Heparin is a sulfated glycosaminoglycan with a molecular weight of 3–30 kD12 and a complex sulfated glycosaminoglycan with a molecular weight of 3–30 kD12. It has an anticoagulant effect indirectly by increasing antithrombin activity. Heparin binds to antithrombin through a particular pentasaccharide sequence, causing a conformational shift in antithrombin that increases its activity with thrombin by 1000-fold13. Heparin is a structurally diverse substance with very varied pharmacokinetics that is generated from swine intestinal mucosa. Only one-third of heparin molecules contain the high-affinity pentasaccharide sequence necessary for the heparin-antithrombin complex14, 15. Due of heparin's strong anionic characteristics, further heparin-thrombin binding might occur electrostatically. Nonspecific binding to other molecules, such as plasma proteins, platelets, and leukocytes16, is caused by this negative charge. To ensure that blood heparin levels are within therapeutic range, close laboratory monitoring is essential.

Argatroban, unlike heparin, is a highly selective, direct thrombin inhibitor that binds to both free and clot-associated thrombin17 in a reversible manner. Suppression of protein C, inhibition of numerous procoagulant factors (V, VIII, XIII), and inhibition of platelet aggregation17, 18 are some of the other antithrombotic qualities. Argatroban has been authorised by the FDA for use as an alternate systemic anticoagulant in individuals who cannot take heparin because to heparin-induced thrombocytopenia19. Procedure anticoagulation for percutaneous cardiac procedures, as well as anticoagulation for extracorporeal membrane oxygenation and renal replacement therapies20–22, are further clinical uses to date.

Although both heparin and argatroban are thrombin inhibitors, argatroban has a number of advantages over heparin. For starters, argatroban is a direct thrombin inhibitor, meaning it doesn't need a co-factor (such as antithrombin) to work. It can also stop thrombin from circulating and binding to clots. Second, argatroban's pharmacokinetics are more predictable since it is a homogenous synthetic compound. Finally, argatroban does not interact with heparin-induced antibodies, therefore it cannot produce heparin-induced thrombocytopenia, an uncommon but possibly severe allergic reaction.

References

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