Sheep (Ovine) Mucosal Heparin as a Substitute for Porcine Mucosal Heparin. A Viable Option to Address the Potential Shortage Crisis.

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Introduction

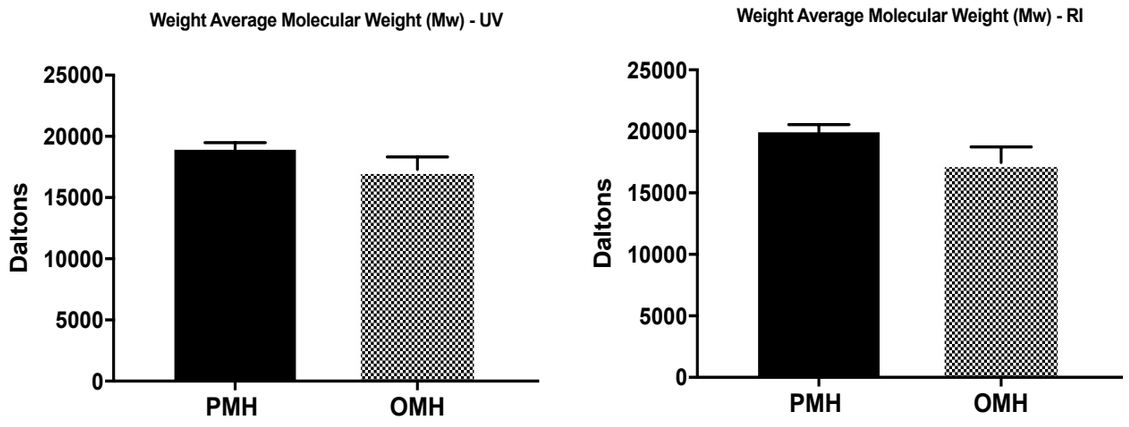
Porcine mucosal heparin (PMH) represents the sole anticoagulant for surgical and interventional procedures along with its medical usage. The current African Swine Fever is of pandemic magnitude and has dramatically impacted on the global population of pigs thus creating a shortage of PMH. Sheep mucosal tissue have been used to prepare heparin which demonstrates biosimilar characteristics to PMH. The aim of this study is to compare multiple batches of sheep mucosal heparin (OMH) with PMH to demonstrate their bio-similarities.

Materials & Methods

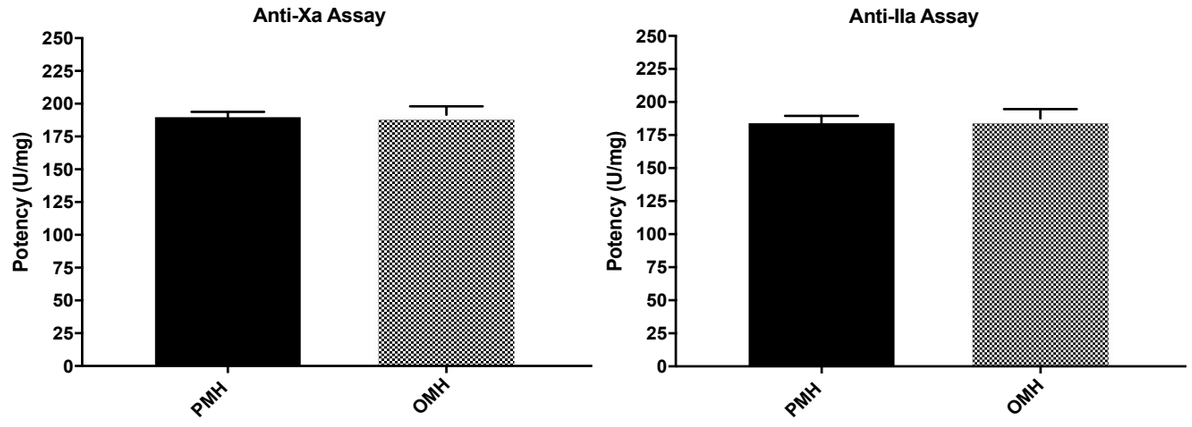
Multiple batches of Sheep (OMH) active pharmaceutical ingredient were obtained commercially (Ronnsi Pharma, Suzhou, China). Multiple batches of PMH were obtained from a supplier (Medefil, Inc, Glendale Heights, IL, USA). Both groups of heparin were evaluated for molecular distribution profile using the HPLC methods and the USP potency using the pharmacopeia approved anti-Xa and IIa methods. The anticoagulant activities were profiled in both the whole blood and plasma-based assays. The neutralization of these groups of heparin with platelet factor 4 and protamine sulfate were studied in various assays. The comparative effects of these agents were studied in the HIT antibody mediated aggregation. The antithrombotic and bleeding profiles were measured in standard animal models. The pharmacokinetics and pharmacodynamics profile was investigated in non-human primates (n=4 for each group) after I.V. injections of drugs.

Figures

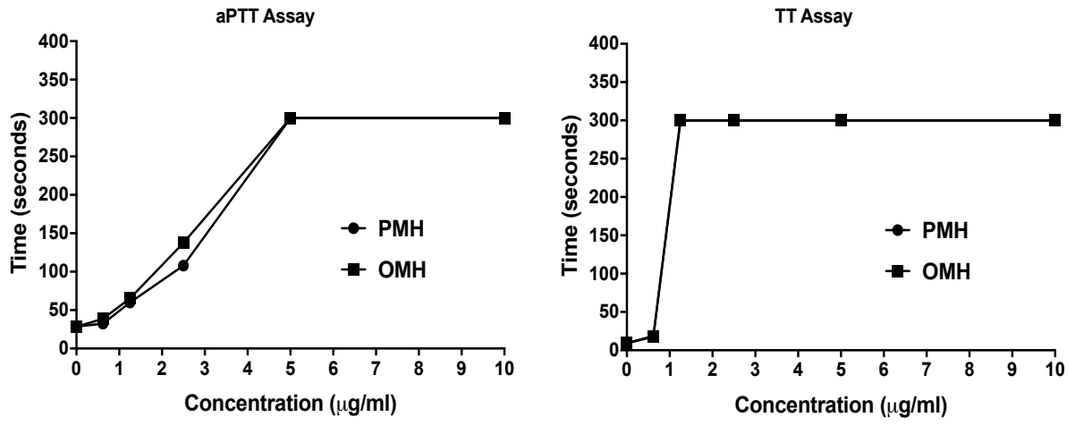
Molecular Weight profiling of sheep mucosal heparin in comparison to porcine mucosal heparin



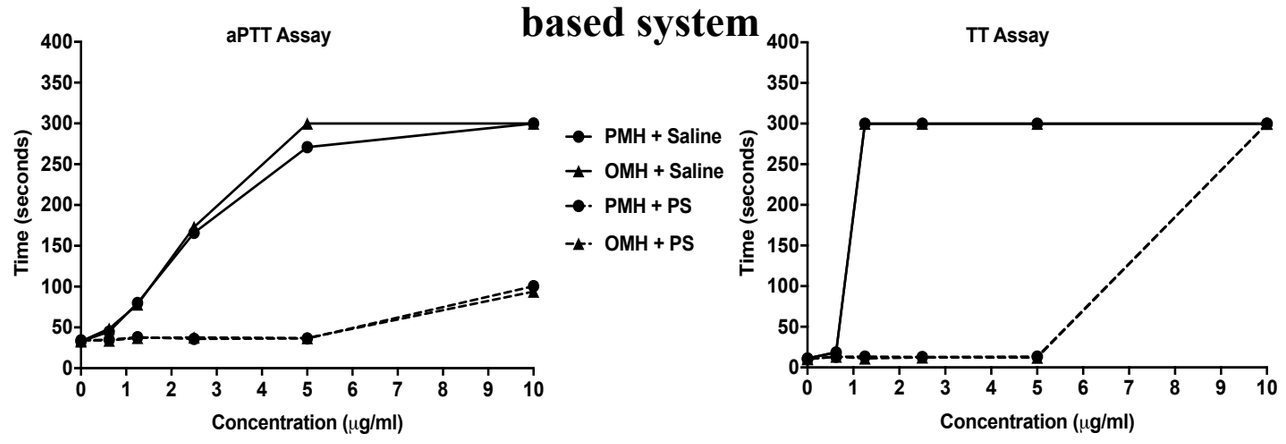
USP potency of sheep mucosal heparin in comparison to porcine mucosal heparin



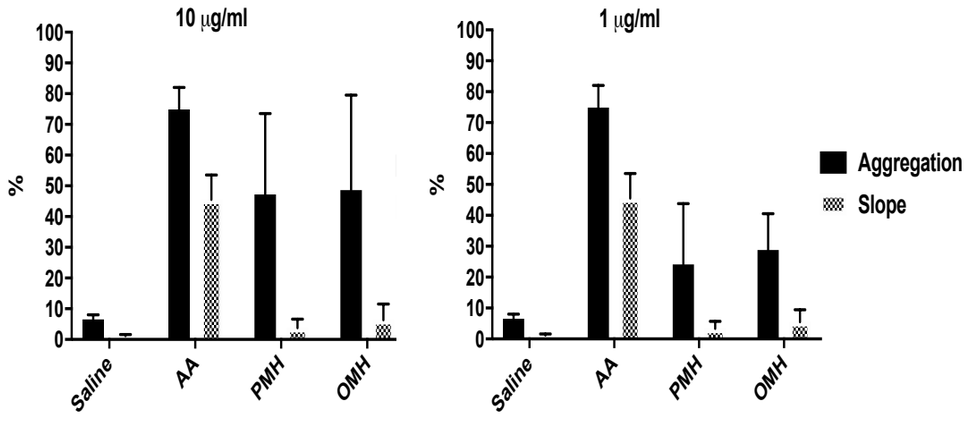
Anticoagulant activities of sheep mucosal heparin in comparison to porcine mucosal heparin in plasma-based system



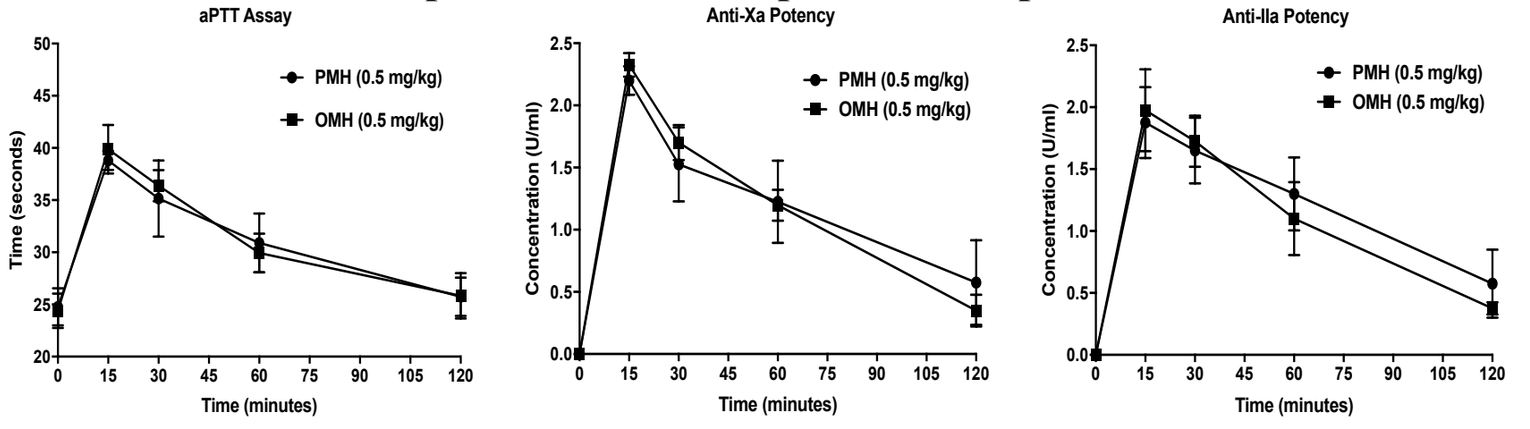
Protamine Sulfate neutralization of anticoagulant activities of sheep mucosal heparin in comparison to porcine mucosal heparin in plasma-based system



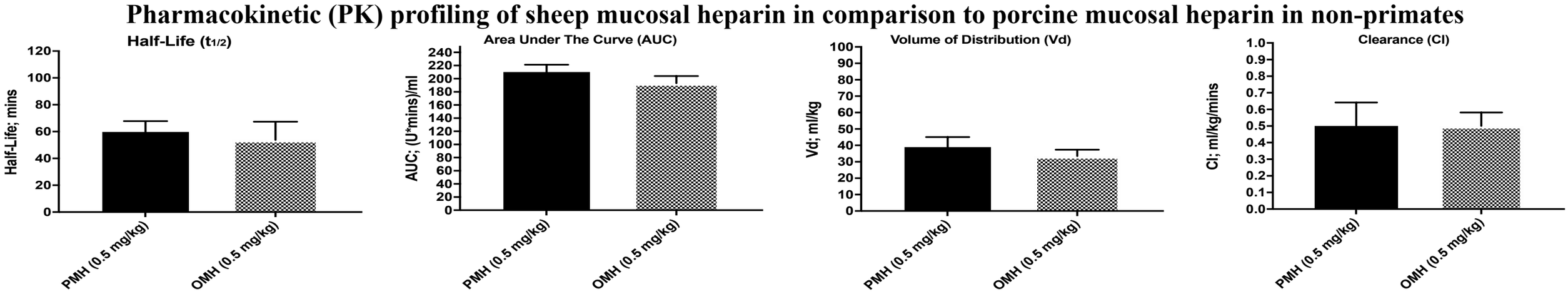
HIT mediated platelet aggregation of sheep mucosal heparin in comparison to porcine mucosal heparin



Pharmacodynamic (PD) properties of sheep mucosal heparin in comparison to porcine mucosal heparin in non-primates



Pharmacokinetic (PK) profiling of sheep mucosal heparin in comparison to porcine mucosal heparin in non-primates



Results

Both the Sheep (OMH) and PMH produced comparable molecular weight distribution profiles. The USP potency of the OMH was found to be 190±7 U/ml in comparison to PMH at 181±8 U/ml. In the ACT and TEG, both OMH and PMH produced comparable effects ($p>0.05$). Both the protamine sulfate and platelet factor 4 produced comparable neutralization of OMH and PMH. In a HIT antibody mediated platelet aggregation assay, no differences were seen in the platelet responses. The bleeding and anti-thrombotic profile of OMH and PMH was comparable. The pharmacokinetic parameters in terms of biologic half-life ($t_{1/2}$), area under the curve (AUC), volume of distribution (Vd), and clearance rate (Cl) were similar ($p>0.05$).

Conclusion

The results demonstrate that OMH and PMH are comparable in producing their anti-coagulant and anti-protease effects. In the USP assays and clot-based assays, they are comparable. Moreover, their anti-thrombotic and anti-coagulant effects are identical. The PK/PD profile is also comparable for the anti-Xa and anti-IIa effects. These results validate the hypothesis that, OMH is bio-equivalent to PMH and can be substituted for PMH products.