

The troubled heparin issue in the Brazilian market and the search for solutions

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In 2008, the world market experienced a troubled period with respect to reliability of the product heparin. In the United States and Europe, lots of non-fractionated heparin were fraudulently contaminated with oversulfated chondroitin, which resulted in death of hundreds of patients. Brazil was also affected by the problem of heparin, but in other way.

In early 2008, after the abrupt withdrawal from the market of non-fractionated endovenous heparin of the Roche laboratory (Liquemine), the Brazilian Society of Cardiovascular Surgery (BSCVS) began to receive alarming increase in queries from cardiac surgeons from around the country about the appearance of complications with the use of other brands of heparin available in the domestic market. These reported complications mostly involved increased postoperative bleeding and appearance of vasoplegic syndrome.

The mobilization of BSCVS began by contact with the Roche laboratory, that reaffirmed the decision to cease the production of endovenous Liquemine. This brand of heparin (manufactured from the intestinal mucosa of pigs) was used by almost all the services of Cardiovascular Surgery of the country and had great reliability. At the same time, the National Health Surveillance Agency (ANVISA) was notified and the appropriate actions were requested.

Then, the BSCVS contacted directly the pharmaceutical companies that market the non-fractionated heparin sodium in Brazil. Eurofarm and Bérigamo laboratories manufacture injectable heparin sodium from raw material (bovine intestinal mucosa) provided by national companies.

The analysis of these products, performed at the Connective Tissue Laboratory of the Federal University of Rio de Janeiro, and additional tests performed in laboratories of the Federal University of Paraná and Federal University of Santa Maria, Rio Grande do Sul, showed no evidence of contamination by oversulfated chondroitin in the product analyzed. It was noted that the quantity of low molecular weight heparin met the reference product specifications.

However, based on this analysis, it was shown clear difference in potency of action between the non-fractionated heparins from different origins, bovine and

porcine – the latter, as the case of Liquemine. The porcine heparins have greater power of action than the bovine ones, with need for dose adjustment and more accurate monitoring when there is change of the product, which may explain the complications observed when the Liquemine was withdrawn from the market [1].

It became obvious that, although safe for use, the heparins made from bovine intestine are not the ideal choice for cardiovascular surgery, unlike those heparins made with pig intestine. Due to the difference in power between the non-fractionated heparins both of bovine and porcine origin, the recommendation from BSCVS was that a more rigorous testing of activated coagulation time (ACT) during heart surgery should be performed in order to ensure that ideal levels of anticoagulation were being achieved.

It was agreed that the pharmaceutical companies, with the support of the ANVISA and BSCVS, would develop the heparin derived from intestinal mucosa of pigs - similar to the product Liquemine that was withdrawn from the market. Four national pharmaceutical companies - Blausiegel, Bérigamo, Eurofarma and Cristália - developed the product heparin, derived from pig intestines. Under quality tests, these porcine heparins showed chemical structure and activity similar to the product Liquemine as study performed at the Connective Tissue Laboratory of the Federal University of Rio de Janeiro, since the raw materials for domestic industries comes from the same chinese pharmaceutical company that provided such material for the company Roche. The Chinese pharmaceutical were inspected by the Food and Drug Administration (FDA) and the ANVISA, that certified the laboratories with the GMP/BPF Good Manufacturing Practices certification.

After long and detailed agreement with ANVISA and national pharmaceutical companies that market heparin in Brazil, BSCVS started a clinical study with those porcine heparins to be marketed in Brazil, with a protocol extensively discussed between the Parties, to ensure quality and standardization of the product to be introduced in the national market.

The clinical study started is being performed in only one center to ensure uniformity of the procedure (Federal University of Campinas - UNICAMP) and will provide clinical

and scientific informations that may be relevant to the knowledge of the product's action, as well as its neutralization by protamine. It is a phase III study, whose primary objective is to verify, by means of randomized, open, parallel, and comparative study, the efficacy and safety of non-fractionated heparin sodium of porcine origin in patients undergoing heart surgery using cardiopulmonary bypass, by controlling of hemostasis during and after surgery, based on measurements of coagulation markers, such as ACT, activated partial thromboplastin time (aPTT) and anti-factor Xa assay on the bioavailable heparin and blood loss. The secondary objective of this study is to evaluate the average dose of heparin sodium used in surgery and its relation with the dose of protamine and the need for transfusions of blood and blood products during and after the procedure. Also, a secondary objective of this study is to evaluate the safety of the use of heparin in relation to type, incidence and rate of adverse events observed during the study period.

In agreement with the Adib Jatene Foundation, the devices for measurement of ACT and the substrate used in such devices will also be assessed so we can have a proper comparison between advanced methods of evaluation of the coagulation and anticoagulation and simple method (ACT) routinely used in operations with cardiopulmonary bypass in Brazilian hospitals.

Finally, the BSCVS would like to emphasize the sense of responsibility and professionalism demonstrated by national pharmaceutical companies, who have undertaken all efforts to develop and supply the national market with porcine non-fractionated heparins for specific use in cardiovascular surgery, eliminating the trouble left by withdrawal of the product Lique mine from the market by the Roche company. Moreover, the action of ANVISA with competent and dedicated professionals who worked closely with the BSCVS and domestic industry, promoted conditions for the rapid return of the product on the market. We also

emphasize the great reception of the BSCVS by ANVISA, that put its trust in our society so that the protocol may be developed and established, showing a partnership that will certainly be beneficial not only in the field of heparins but in others on which BSCVS, as authentic representative of Brazilian cardiovascular surgeons, may assist in the qualification of all supplies we used.

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