Heparin pharmacovigilance in Brazil

Daniela Rezende Garcia Junqueira[1], Thércia Guedes Viana[2], Eliane R. de M. Peixoto[3], Fabiana C. R. de Barros[3], Maria das Graças Carvalho[4], Edson Perini[5]

[1] M.Sc., Ph.D. Student in Pharmaceutical Sciences, Universidade Federal de Minas Gerais (UFMG); Contributor Investigator, Centro de Estudos do Medicamento (Cemed), Pharmacy School, UFMG, Belo Horizonte, MG, Brazil
[2] Pharmacyst; M.Sc. Student in Biological Sciences, Physiology and Pharmacology, UFMG; Contributor Investigator, Cemed, Belo Horizonte, MG, Brazil
[3] Pharmacyst; Contributor Investigator, Cemed, Belo Horizonte, MG, Brazil
[4] Ph.D. in Hematology; Full Professor, Department of Clinical and Toxicological Analyses, Pharmacy School, UFMG, Belo Horizonte, MG, Brazil
[5] Ph.D. in Epidemiology; Associate Professor, Department of Social Pharmacy, Pharmacy School, UFMG; Coordinator, Cemed, Belo Horizonte, MG, Brazil

Summary

Objective: To investigate the biological origin of injectable unfractioned heparin available in Brazilian market by discussing the impact of the profile of commercial products and the changes in heparin monograph on the drug safety. **Methods:** The Anvisa database for the Registered Products of Pharmaceutical Companies and the Dictionary of Pharmaceutical Specialties (DEF 2008/2009) were searched. A survey with industries having an active permission for marketing the drug in Brazil was conducted. **Results:** Five companies were granted a permission to market unfractioned heparin in Brazil. Three of them are porcine in origin and two of them are bovine in origin, with only one explicitly showing this information in the package insert. The effectiveness and safety of heparin studied in non-Brazilian populations may not represent the Brazilian reality, since most countries no longer produce bovine heparin. The currently marketed heparin has approximately 10% less anticoagulant activity than that previously produced and this change may have clinical implications. **Conclusions:** Evidence about the lack of dose interchangeability between bovine and porcine heparins and the unique safety profile of these drugs indicates the need to follow the treatment and the patients' response. Events threatening the patient's safety must be reported to the pharmacovigilance system in each particular country.

Keywords: Heparin; anticoagulants, product surveillance; drug monitoring; drug toxicity.

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Correspondence to:
Daniela Rezende Garcia Junqueira
UFMG, Faculdade de Farmácia
Depto. de Farmácia Social
Centro de Estudos de Medicamento (Cemed)
Av. Antônio Carlos, 6627, sala 3111 B4
Campus Pampulha
Belo Horizonte – MG
CEP: 31270-901
danirgj@terra.com.br

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Introduction

Heparin is a natural agent with an anticoagulant action. The drugs commercially available are isolated and extracted from porcine intestinal mucosa and bovine pulmonary tissue. Heparin isolation and extraction process leads to partial degradation of glycosaminoglycan chains that make it up[1], producing a drug composed of molecular fragments with heterogeneous molecular weights, ranging from 3,000 to 30,000[2], and known as unfractioned heparin (UFH), standard heparin or simply heparin. Heparin pharmacokinetic and pharmacodynamic properties also show great heterogeneity due to different anticoagulant potencies of action presented by fractions with distinctive molecular weights and also due to heparin binding to plasma cells and proteins.

Another type of commercially available heparin, the low molecular weight heparin (LMWH), is made up of molecular fragments with average molecular weight 5,000 and it is obtained by acid depolymerization of standard heparin[3]. As different depolymerization methods are available, there are different low molecular weight heparins[2]. LMWH preparations have more predictable pharmacokinetic and pharmacodynamic properties, thus being more convenient than UFH when used in different clinical settings[2]. Actually, in several countries, LMWHs are replacing UFH. In Brazil, however, several clinical interventions are still UFH-dependent[4]. Furthermore, in Brazil, the delivery of heparin from both available animal sources is still remaining, whereas in the United States and in Europe bovine UFH is no longer produced because of the bovine spongiform encephalopathy epidemics[5,6].

In 2008, a contamination in batches of UFH marketed by Baxter Healthcare, a major producer of the drug in several countries, brought out a serious world crisis in heparin market[6]. The contaminant identified, the oversulfated chondroitin sulfate, is a substance similar to heparin and its administration brought on reactions characterized by hypotension, nausea and respiratory distress, occurring within 30 minutes of exposure[6]. These reactions were associated with over 200 deaths in several countries[7]. In Brazil, the international crisis was added to the unexplained market withdrawal of the intravenous unfractioned heparin by Roche (Liquemine) in 2007[4].

The crisis caused by the heparin contamination culminated with several changes in clinical and drug production actions. In a global level, the heparin monograph was revised by the United States Pharmacopoeia (USP) and by the World Health Organization aiming to introduce quality tests able to detect the oversulfated chondroitin sulfate which were not previously contemplated[7,8]. In Brazil, heparin shortage stimulated a market restructuring, with the introduction of new suppliers and consequently new raw material sources for the product[4,9,10]. All these changes impact heparin pharmacovigilance, introducing new safety issues regarding therapy vigilance in UFH anticoagulation. In view of these issues, the objective of this study was to investigate the biological origin of injectable heparin preparations which are available in Brazilian market, discussing the impact of the profile of commercial products and the changes in heparin monograph on the drug pharmacovigilance.

Methods

In order to determine the biological origin or UFH injectable preparations in Brazil, the Anvisa database for Registered Products of Pharmaceutical Companies of the National Health Surveillance Agency (Anvisa)[11] was searched to identify pharmaceutical companies with a permission to market the drug in the country. In addition, the Dictionary of Pharmaceutical Specialties (DEF 2008/2009) was also consulted. The companies identified with an active permission for the drug trade were initially contacted by telephone via Consumer Attendance Service (SAC) and via e-mail later. The contact with the companies followed a standardized form with the purpose of addressing the following topics: kinds of heparin currently produced by the company if any; commercial name and formulation of the product; main commercial destination of the drug (hospital or drugstores), and biological origin of the heparin.

The survey was conducted between August 19 and September 28, 2010 by the team of the Drug Study Center of the *Universidade Federal de Minas Gerais,* Pharmacy School (Cemed – UFMG).

Results

Nine trademarks filed with Anvisa were identified and they concerned eight pharmaceutical companies manufacturing heparin as an injectable formulation. One of the companies could not be located by the available references and was excluded from the query. Out of the eight trademarks whose producer company could be contacted, one (Heparin™), is no longer produced, having been replaced by another product (Hemofol™) by the same producer laboratory. Among the remaining trademarks, two have a registration expired with Anvisa and they are in a process of permission renewal (manufacturer's information) and three companies have an active permission to market heparin in Brazil.

Among the products with an active license or in a renewal process, three consist of an injectable formulation for a subcutaneous route administration (3/5), one consists of a formulation for intravenous administration (1/5) and one is a formulation intended for either subcutaneous or intravenous administration (1/5).

Regarding the biological origin of the drugs, three (60%) are porcine in origin and two (40%) are bovine in origin, with only one having this information explained in the package insert. Out of the five pharmaceutical companies

producing heparin in Brazil, four market their products only to hospitals and one to both hospitals and drugstores.

The commercial names of the drugs identified, as well as the raw material biological origin, the available pharmaceutical formulations and the main commercial destination of the products are summarized in Table 1.

Discussion

The pharmacovigilance, the Phase IV in drug clinical studies, comprises activities related to detection, evaluation, understanding, and prevention of adverse events or any issues related to the drugs with the purpose of identifying risks and preventing damage to patients[12]. Various aspects of the drug post-marketing period are of interest to pharmacovigilance, including continued efficacy review, adverse reactions, adverse events from quality deviation, off-label use, drug interactions, therapeutic ineffectiveness events, poisonings related to drugs and also potential or actual medication errors[13,14].

Although UFH has been the major tool in managing thromboembolic conditions for over 50 years[15], the drug has aroused great interest to the pharmacovigilance system as a function of recent commercial and clinical circumstances, demonstrating a necessary warning regarding its use.

UFH biological origin is a seldom explored factor in the guidelines of the drug dose and dose regimen. However, the drug animal source changes its effectiveness and safety profile[16,17]. Actually, bovine heparin and porcine heparin are not equivalent drugs[16]. Bovine heparin has a higher sulfatation degree of its compounds and this determines distinct effects from porcine heparin regarding coagulation, thrombosis, and bleeding. Bovine heparin also differs in its affinity for protamine, a substance used in the drug anticoagulant effect inhibition. All of these issues can show the lack of dose interchangeability between bovine and porcine heparins, thus stressing the need of treatment monitoring. Thus, the UFH biological origin may affect effectiveness and safety aspects of the therapy upon using the drug. The issue assumes a particular relevance when we observe this information is commonly missing in drug labels and drugs with different biological origins are simultaneously and interchangeably marketed in Brazil.

LMWHs, in turn, are not affected by the drug biological origin aspects because bovine heparin is not used in their production due to possible viral contaminants, such as those in bovine spongiform encephalopathy[15].

The recent crisis in heparin market gave rise to another issue with a global impact, stressing the warning regarding UFH use: changes in the drug monograph. All products marketed in Brazil and in the world must be submitted to the new recommendations established in UFH monograph by the World Health Organization and the United States Pharmacopoeia aiming to assure the safety and quality of active pharmaceutical ingredients[7,8,18]. The amendments foresee the introduction of additional tests which must be used by producers to identify contaminants and the implementation of a new potency assay. The new recommended potency test, the anti-factor IIa chromogenic assay, offers higher additional specificity and safety against potential adulterants mimicking heparin activity. In parallel with the new test introduction, a new potency reference standard was also defined[8]. In addition, the heparin potency unit used by the United States Pharmacopoeia was harmonized with the International Unit (IU) used by the World Health Organization.

Although the changes in heparin monograph have contributed to a safer and higher quality product, the question remaining is the clinical significance of the drug potency change. Studies conducted by the agency regulating drugs in the United States, the Food and Drug Administration (FDA), demonstrated heparin produced in accordance with the new specifications in the USP monograph was approximately 10% less active as an anticoagulant than the heparin previously produced, which stresses potency changes may have clinical implications in certain settings, such as the *in bolus* intravenous administration[19]. Yet USP, responsible for the new monograph, does not anticipate the potency change shows any clinical relevance[20].

Table 1 – Unfractioned heparins marketed in Brazil according to the commercial name, raw material biological origin, pharmaceutical formulations and main product commercial destination

Commercial name	Biological origin	Pharmaceutical formulations	Main commercial destination
Actparin	Bovine	5,000 UI/mL (IV) 5,000 UI/0.25 mL (SC)	Hospitals (IV and SC) Drugstores (IV)
Hemofol	Porcine	5,000 UI/0.25 mL (SC) 5,000 UI/mL (IV)	Hospitals
Hepamax-s	Porcine	5,000 UI/mL (IV e SC)	Hospitals
Heptar	Bovine	5,000 UI/mL (IV)	Hospitals
Parinex	Porcine	5,000 UI/mL (IV) 5,000 UI/0.25 mL (SC)	Hospitals

IV, intravenous route; SC, subcutaneous route

Regardless the diverging views about the clinical impact of the new heparin potency, the need of a careful clinical follow-up of the drug effect and the patients' response to the "new" medication[7,8,19] is a consensus. Any suspicious changed response must be evaluated and spread to the community through a report to the responsible department[19,20].

Among the adverse events of interest to pharmacovigilance, adverse drug reactions should be highlighted, as they are on the base of great disasters related to medication use in populations and because about half of drugs are known to induce adverse reactions detected only in the post-marketing phase (pharmacovigilance)[13]. Heparin-induced adverse reactions include hemorrhage, anaphylactic reaction, liver enzyme elevation, osteoporosis (over a long time of use) and heparin-induced thrombocytopenia (known as HIT)[21]. Heparin-induced hemorrhage and thrombocytopenia are pointed out for their frequency and severity.

Bleeding associated with heparin use may occur in any site and they are incident in frequencies between 5% and 10%[21]. Actually, hemorrhage is a known risk with heparins, being an extended therapeutic action of the agent. Bovine heparin use increases this hemorrhage risk because the doses required to induce bleeding seem to be lower than those with porcine heparin[16]. Heparin-induced hemorrhage adverse reactions must therefore be reported to the pharmacovigilance system, always including the drug biological origin into the event report. This information allows the appropriate understanding development about this subject and the risk epidemiologic profile establishment of heparins marketed in Brazil.

Heparin-induced thrombocytopenia is a frequent and potentially fatal immunodependent adverse reaction[22-24]. A major consequence is the increased paradoxical risk of thromboembolic complications. This reaction understanding is still improving. Its incidence is known to be variable, depending on the heparin type used, whether UFH or LMWH, as well as the patient population exposed[17]. The subgroup with the highest risk includes patients using UFH postoperatively (1% to 5%). The reaction incidence is variable according to the UHF biological origin, with bovine heparin being more immunogenic than porcine heparin[17].

In Brazil, heparin-induced thrombocytopenia incidence remains unknown, as well as its clinical implication severity. This is worrisome, considering the differences of UFH marketed in Brazil: while most countries do not produce bovine heparin, 40% of products delivered to our market are this kind of heparin. Thus, knowledge based on data about this reaction produced in markets and populations in other countries may not represent our reality. Given this issue relevance, which is demonstrated by several studies in other countries, notably in North Hemisphere countries, as well as the frequency and potentiality for the development of major clinical events resulting from heparin-induced thrombocytopenia, this is a worrying gap in our pharmacovigilance system.

The lack of knowledge about the HIT epidemiologic profile in Brazil can further be associated with an important economic impact. Every 15 new cases recognized per year costs the institution between 700,000 and 1.8 million dollars[25]. On the other hand, the reaction clinical non-recognition may result in improper treatments, increased life or amputation risk and a further increase in financial and life cost.

In Brazil, Anvisa has been expanding its activities in pharmacovigilance and currently the sector has an improved and efficient online reporting system[26]. Health practitioners, users and the pharmaceutical industry are stimulated to feed the system and collaborate with safe and effective use of drugs marketed in the country.

Conclusion

The evidence about the lack of dose interchangeability between bovine and porcine origin heparins, the unique safety profile between these agents and the permanence of heparins produced from different animal sources in Brazilian market indicate the need of treatment and patient response follow-up. Heparin effectiveness and safety studied in non-Brazilian populations may not represent Brazilian reality, since most countries do not produce bovine heparin and the heparin currently marketed is approximately 10% less active as an anticoagulant than that previously produced, this change can have clinical implications. The need of clinical studies to test the safety and efficacy of heparin formulations used in Brazil is highlighted. The pharmacovigilance system must be communicated about events threatening the patient's safety.

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