Heparin is an anticoagulant that is commonly administered intravenously or subcutaneously and primarily used in the treatment or prevention of other serious medical conditions, including deep venous thrombosis and pulmonary emboli. Heparin is available in different strengths and is widely used in concentrations of 1000 units/mL or greater. Currently, worldwide heparin sales are estimated to be more than $4 billion. Baxter Healthcare Corporation is one among the four marketing authorization holders and a major supplier of heparin in the United States (U.S.).

Hematological adverse events to heparin are common while sensitivity reactions and local adverse effects are rare. Baxter Healthcare Corporation used to receive about 60 to 70 adverse reaction reports per year for heparin. In 2008, by January itself Baxter received 150 adverse reaction reports. Because of the increase in number of adverse reaction reports, on January 17, 2008, Baxter voluntarily recalled nine lots of heparin (30mL and 10mL vials of 1000 units/mL) from the US market. Baxter continued to sell the other lots of their heparin.

A contaminant, a large complex molecule chemically similar to heparin, was detected in heparin samples from a Chinese and a US plant, both owned by Scientific Protein Labs (SPL). The active pharmaceutical ingredient (API) contained in Baxter’s heparin vials was supplied by SPL. The US Food and Drug administration (FDA) reported that 20 of the 28 lots of heparin API tested from the Changzhou plant of SPL were contaminated. The FDA admitted that it had never inspected the Chinese plant that supplies heparin to Baxter and alerted the public about serious adverse events reported to Baxter’s heparin vials. The FDA requested Baxter to provide the records of audits performed on their API suppliers’ manufacturing sites. The FDA then inspected the manufacturing facility of SPL at Changzhou, China and made 11 observations during the inspection, these were notified to SPL in FDA Form 483 (form for inspectional observations). The FDA issued a warning letter to Changzhou SPL Company Ltd. On 28th February, Baxter recalled all the remaining lots of heparin vials from the market.

All reported adverse drug events to heparin occurred in three specific areas of product use: renal dialysis, invasive cardiovascular procedures and apheresis procedures. Various types of adverse drug reactions were reported. Some of these reactions, particularly profound and refractory hypotension, anaphylactic-type reactions, acute gastrointestinal distress and hemorrhage were serious or life-threatening. Forty per cent of the cases reported to the US FDA were estimated as serious. A review of the adverse event reports to heparin by the FDA from 2006 to 2008 revealed 169 deaths between October 2007 and March 2008. One hundred and ten deaths were due to one or more allergic/hypotensive symptoms [Figure 1]. In 2006, among the total 55 death reports received by the FDA, only three death reports were due to allergic/hypotensive symptoms. Since Baxter’s expanded recall, the number of deaths related to allergic reactions to heparin returned to the baseline levels.

China’s state food and drug agency confirmed that the contaminant in Baxter’s heparin was sourced from China. The FDA identified the contaminant as over-sulfated chondroitin sulfate (OSCS). Some batches of heparin vials were reported to contain as much as 50% of OSCS. Chondroitin sulfate is a cheaper substitute. Sulfate is added to chondroitin to make it similar to heparin. This modified heparin is difficult to identify in routine screening tests. Scientific Protein Labs informed that OSCS could have entered from infected pigs used for obtaining the heparin instead of healthy pigs. Was the contaminant introduced intentionally? This is not yet clear.

By March 6, 2008, heparin recall was announced in Germany after 100 adverse events were reported. As a precaution, by March 11, 2008, three Japanese companies recalled heparin that had been sourced in China even though there was no increase in frequency of adverse effects. By the end of March, recalls were also observed in France, Italy and Denmark. Till date, 11 countries have reported the presence of contaminated heparin.

The FDA requested the manufacturers of low molecular weight heparin (LMWH) to test their product and API for OSCS as heparin forms the source for LMWH. Testing of these products by various manufacturers revealed some contamination by OSCS. By the end of April, 2008, Australia, Sweden and Italy requested the recall of contaminated lots of enoxaparin (a LMWH).
The FDA conducted an intensive immunologic investigation to look into the mechanism of these reactions. The evaluated in vitro and animal data provided a concrete mechanistic link between OSCS and the adverse reactions observed after bolus dosing of heparin.\cite{22,24,25} The FDA and the US Pharmacopoeia have agreed to develop compendial tests on an expedited basis to enable heparin manufacturers to detect the presence of trace amounts of OSCS.\cite{17}

All this happened because of both manufacturers and regulators being vigilant and good pharmacovigilance system of these countries. Also, all the developments happened in a time period as short as approximately 14 weeks. When we think of addressing this issue in the Indian scenario, several questions arise: can this occur in India? Alternatively, has it already happened and has gone unnoticed? Do the manufacturers and suppliers of heparin in India collect the adverse reaction reports and analyze them till their product’s existence in the Indian market as it was done by Baxter in the US? Where do Indian suppliers source heparin API from? Does the heparin marketed in India contain OSCS? Where do Indian suppliers source heparin API from? Does the health authority assess the adverse drug reactions to heparin reported to the National Pharmacovigilance Programme (NPP) and encourage healthcare professionals to report all reactions to heparin.

Regulatory authority
- Should immediately assess the adverse drug reactions to heparin reported to the National Pharmacovigilance Programme (NPP) and encourage healthcare professionals to report all reactions to heparin.
- Should invite and support the peripheral pharmacovigilance centers (PPCs) to perform prescription event monitoring for heparin and report all adverse drug events, as a special case, directly to the national center than through regional and zonal centers to quickly generate the safety data.
- Should ask the manufacturers/suppliers of heparin in India for such adverse drug event reports. Also, should demand to test their products for OSCS or regulatory authority on their own should sample and test the marketed heparin in the country. If OSCS is identified, should immediately notify the respective organizations to recall their products.
- Should work in close contact with the US FDA and pass on the contamination-screening test to all the manufacturers and suppliers of heparin. Also, should incorporate this test in Indian pharmacopoeia.
- Should consider extending the period of periodic safety update reports to all the drug products till their existence in the Indian market.

Manufacturers and suppliers of heparin
- Should sample and test their API and heparin products manufactured and already in the market for OSCS and voluntarily recall the batches if the contaminant is tested positive.
- Should call for the reports of adverse drug events to heparin from those who prescribe their brands and forward all the reports immediately to the regulatory authority.

Healthcare professionals
- Closely monitor the patients who are receiving heparin for adverse events, particularly, but not limited to anaphylactic-
type reactions, acute hypotension, acute gastrointestinal distress, thrombocytopenia, excessive anticoagulation or hemorrhage and inadequate anticoagulation and report any suspected reaction to PCCs and manufacturers.

- Should continue to prescribe heparin with careful observation so that the benefit of this life-saving drug is given to needy patients.
- Should alert and educate the patients of the adverse drug events to heparin.

An international medication safety issue can be investigated in a short time only by the combined efforts of regulatory authority, manufacturers and healthcare professionals. Pharmacovigilance is in its ‘infancy’ in India but it is not ‘new’. A decade ago, India joined the World Health Organization (W HO) international drug-monitoring program. National Pharmacovigilance Program (NPP) was officially launched in November 2004. Traditionally very little is done to address drug safety issues in India by pharmaceutical companies. Implementation of amended Schedule ‘Y’ of the Drugs and Cosmetics Act, has not improved the situation yet. The NPP has achieved very little, if anything, until now. A lot needs to be done to put in place a pharmacovigilance system robust enough to verify such important medication safety signals as observed in case of heparin. Also, we are way behind the western countries in identifying safety signals to new drugs and quantifying the risks.

The Ministry of Health, Govt. of India should take immediate measures to strengthen the NPP in an effort to provide a safer healthcare system for the country. Private public partnerships, industry institution interaction, involvement of professional bodies like the Indian Medical Association, integrating pharmacovigilance in public healthcare system are important. Providing enough funding and necessary infrastructure to the regulatory authority and training them in the aspect related to pharmacovigilance should be addressed on priority. We should look beyond a pharmacovigilance program limited to regulatory purpose and registration of pharmaceuticals and strive to establish a healthcare-focused pharmacovigilance system.

References


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