Contaminant in the Recalled Unfractionated Heparin Preparations: Where is the Problem?

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March 10, 2008/ 4:38 p.m. (EST): In a recently held press conference, the USFDA briefed the press that the potential contaminant in the recalled Baxter product is a heparin-like substance. The USFDA commented that utilizing high tech methods heparin-like molecules have been identified. No specifics regarding these contaminants were given. The Baxter personnel did not agree with this interpretation. The manufacturing process of heparin is such that other heparin-like contaminants such as the dermatan sulfate, heparin sulfate, and chondroitin sulfate are removed effectively. These represent the main contaminants in heparin.

However, the usual contaminants are unlikely to produce any allergic effects and produce the reported adverse reactions. Because of the carbohydrate nature of the contaminants identified in the special method known as the nuclear magnetic resonance technique (NMR), it is quite disturbing to note that such a contaminant may have been added to the recalled heparin or heparin like materials are also isolated from the shellfish, marine plants, bones, skin of mammalian origin. There are various proteins contaminants that can be expected along with the carbohydrates. Thus, it is likely that besides the carbohydrate contaminants, some unknown protein contaminant may also be present in these products.

The statement that a heparin-like material was identified using high tech methods is ambiguous and misleading. Such statements should be specific and clear regarding the nature of the contaminant detected. It is very unlikely that such contaminants as dermatan sulfate, heparan sulfate or chondroitin sulfate, which are the most likely contaminants in heparin, are responsible for the reported complex adverse reactions and/or death in patients treated with heparin. It is quite conceivable that excessive amounts of degradation products and chemically modified sugars maybe present resulting in unusual signals in some
of the methods used to analyze these products.

Glucosamine sulfate is a representative building block of heparin and related agents. It is widely present as a structural component of the products isolated from mammalian tissue and shellfish. Based on the limited information, and the reported adverse reactions, it is likely that the possibility of bacterial contaminants such as endotoxin and other toxic bacterial products may also contribute to the observed adverse effects. It is prudent to test the recalled products for these contaminants. The inspection by the US FDA has already identified various deficiencies in the plant responsible for producing and processing the related heparins. Heparin is extracted from porcine mucosa. The proper processing of mucosal including the initial cleaning and extraction represent important steps in the manufacturing process of heparin. It is at this stage trace amounts of bacterial cellular products, toxins and other undesirable contaminants can be incorporated with the products. The pharmacopeial methods used for the potency of heparin such as the sheep blood recalcification time and pyrogen testing of the finalized products are not capable of detecting these contaminants. It is important that a comprehensive testing of these products for the potential trace protein contaminants is also considered.

The USFDA has stated that the recalled batches contain somewhere from 5-20% heparin-like contaminants. It is highly unlikely that the standard manufacturing process may result in such a high degree of contaminants. The most likely cause of these may be mixing of batches or intentional mixing of heparin like substances. This may be an oversight issue.

While techniques such as capillary electrophoresis and NMR are useful in identifying carbohydrate impurities, these methods do not detect trace protein contaminants, which maybe helpful in identifying the source of the contamination such as marine allergens. This is a reflection of the complexity of the heparin structure and the need for methods to assure the quality of the product. There are no controls at this time except for the pharmacopeial assay specifications, which are stated, in biologic units.

We believe that the public statements from the FDA and Baxter are not clear and that supportive information should be provided. Both have the responsibility to provide clear information on this matter. Moreover, there appears to be a difference of opinion on the origin and nature of contaminant between the regulatory bodies and the suppliers. Because of the magnitude of the severe adverse reactions, it is likely that multiple factors may be responsible for the reported adverse events and deaths related to the use of recalled heparins. Therefore, unless a definitive cause and effect is established, such statements are premature.

Bacterial contamination during the final fabrication of unfractionated heparin has also been reported. This issue may be more complex than what has been stated.
Regardless, it has a major public health impact. It is not acceptable that such problems should arise from poor quality assurance at the bulk material supplier level and sub-standard practices at the fabrication sites. These should have been addressed. We have not had this problem previously and it’s only because of the increased demand for heparin to manufacture LMWHs that such problems are encountered.

Similar allergic reactions and two deaths have been reported from Germany recently, and as a result, the German regulatory agency has recalled the unfractionated heparin from RotexMedica. The source of RotexMedica heparin is also a Chinese supplier suggesting that the problem is related to the manufacturing of the heparin preparations. As a result, the European Community countries have cautioned responsible parties to monitor patients’ anticoagulated with heparin of imported origin. Therefore, this issue has become a global problem, which should be addressed at the World Health Organization level.

The USFDA’s statement that 5-20% of heparin like substances are found in the recalled heparin only points out to the failure of current quality assurance methods in determining non-heparin contaminants in heparin preparations. It doesn’t provide any information on the relevance of these contaminants to the observed adverse effects. If the USFDA believes that these substances are responsible for the adverse effects than a clear approach to isolate these and test these agents for the potential adverse effects in animal models may be essential.

Unfractionated heparin, used in the US and Europe, represents the most widely used anticoagulant for various indications, such as hemodialysis, apheresis and surgical procedures, and has been used for these indications for a long time without any problems. Although isolated incidences of heparin allergy and adverse reactions have been reported, the frequency of recently reported reactions and death are alarming and represent a public health issue. Heparin is a biologic product of complex nature and the likelihood of contaminants in substandard products may cause various adverse reactions. The heparin currently available in the US and Europe is mostly extended from the raw material/finished products originating in China. Recently, several reports have noted the substandard quality of imported heparin preparations. Moreover, reports on the health of live stock imperative in drug and food products have also been published. Recently, the Chinese swine population has suffered from blue ear syndrome. The importance of animal health on the food and drug products cannot be ignored.

The suppliers of heparin, regulatory bodies, and pharmacopial organizations are primarily responsible to enforce proper quality assurance and oversight in assuring the quality of heparin, or other drugs which has been used for over half a century. Simply stating that the recalled products contain 5-20% heparin like structures is misleading and irresponsible. The ongoing problems with the use of
heparin require a comprehensive investigation and may have additional implications on the production of all of the other heparin related drugs.

Addendum: March 18, 2008; 5:18 p.m. (EST): In reference to Dr. Hoppensteadt’s editorial on the contaminants in heparin, preliminary studies on the Baxter’s heparin lots used in the hemodialysis unit of Loyola University Medical Center have revealed the presence of a high molecular weight contaminant in heparin which is not digestible by heparinase I. Additional studies on the digestion of this substance with chondroitinas suggest that this may be a modified form of chondroitin sulfate such as the hyper-sulfated form. Additional studies are needed to further characterize this substance. Since this contaminant is found in heparin’s used at Loyola where no adverse reactions were reported, it is unlikely that this contaminant is responsible for the observed adverse reactions. However, the delayed effect in terms of antibody production in response to this unique material cannot be ruled out.

Contaminated Heparin: An Update

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April 4, 2008; 11:10 p.m. (EST): The current issues related to Heparin have been addressed by both the scientific and clinical community in a stepwise fashion. This situation has resulted in implementing additional compliance regulations and oversight to assure the quality of Heparin and related drugs. Regulatory bodies around the world have already taken initial steps to assure that the quality of Heparin meets the original specifications and is free of any contaminants, such as the reported Hyper sulphated Chondrotin sulphate. The proposed methods to analyse the active pharmaceutical ingredients (API) for the presence of nonheparin

Glycosaminoglycans is the first step in assuring the quality of Heparin. With the advances in analytical methods, including the use of PCR technology, the presence of other biologic contaminants can also be readily checked. As low molecular weight heparins (LMWH) are manufactured using porcine mucosal heparin, source verification is also mandatory. The same methods can be used to check the LMWHs for potential contaminants. With a biologic and complex drug such as heparin, the possibility of contaminants and carry over substances can be expected. However, with modern technology, pure heparin preparations can be readily obtained. Heparin has withstood the test of time and the current crisis will gradually fade away, making this irreplaceable drug available without concern.

In the event of a heparin shortage, alternate agents such as the parenteral antithrombin agents (e.g. argatroban and bivalirudin) are available for surgical and procedural anticoagulation. Other agents such as arixtra may not be useful
for these indications because of the lack of anticoagulant activities. Similarly, the newly developed synthetic oral antiXa and antIIa agents are not useful for acute anticoagulation. Replacing Heparin for acute anticoagulation may not be an easy task and will take some time.

Heparin has been a life saving anticoagulant for decades. The low molecular weight heparins represent a refined use of heparin. The current issue related to the presence of the unusual contaminant is an unfortunate situation, which has stirred up a major controversy. This may be partly due to an increased demand for this anticoagulant resulting in compromised production procedures and increased yield from the sources utilizing alternative approaches. Unfortunately, this has resulted in major adverse reactions and deaths. Regardless of this situation, if manufactured and quality assured properly, the drug would remain the anticoagulant of choice. The current issues eventually will be resolved as these stem from non-compliance and deviation from standard procedures. A more astringent oversight by regulatory bodies and suppliers of heparin will eventually resolve this issue. The attached slides are provided as a briefing on the ongoing issues with heparins and their resolutions. These slides will be periodically updated to include additional information on the developments related to this issue.