



PIC QUESTION OF THE WEEK: 6/17/08

Q: What is the basis for the recent voluntary recall of heparin products?

A: Contamination of heparin solution has become a recent focus of intensive FDA investigation. Heparin sodium was approved in 1939 and has served for decades as the standard parenteral anticoagulant. The drug's most significant adverse effect is hemorrhage. Heparin-induced thrombocytopenia (HIT), frequently associated with thrombosis, is now appreciated as an additional complication of treatment. Between January 1, 2007 and April 13, 2008 the FDA received 131 reports of fatalities related to the administration of heparin. One-hundred and twenty three of these cases were submitted via the MedWatch program on or after January 1, 2008. This spike in reported deaths prompted the FDA to begin an investigation to identify the cause of these events. The agency was able to trace the source of the problem to a major supplier of heparin, Scientific Protein Laboratories, based in Changzhou, China. Although chondroitin sulfate can be identified in trace amounts in heparin products, *oversulfated* chondroitin sulfate (OSCS) is not normally present. OSCS possesses many of the characteristics of heparin and may be difficult to distinguish from the natural product. This contaminant was found in excessive quantities in crude heparin supplied by the company and in the heparin injections associated with these fatal reactions. OSCS directly activates the kinin-kallikrein pathway resulting in generation of bradykinin, a potent vasoactive mediator. Bradykinin can induce hypotension, angioedema, bronchospasm, dyspnea, flushing, abdominal pain, and diarrhea. Many of the MedWatch reports, both fatal and non-fatal, described hypotension, angioedema, and other allergic-like symptoms as part of the reaction associated with heparin. Urticaria and pruritus were rarely reported, suggesting that the reaction was not mediated by antibodies. Baxter Laboratories, which produces 50% of the heparin supplied in this country, suspended its manufacturing and distribution of the drug in February, 2008. Globally, over a dozen other heparin manufacturers voluntarily recalled their products as investigations ensued. Although OSCS has been identified in some batches of enoxaparin distributed in Europe, the quantities were not considered to be significant. Voluntary recalls have led to shortages of heparin and heparin-coated products (e.g. stents) in the healthcare industry. The FDA and Baxter Laboratories continue to aggressively explore this problem associated with heparin contamination.

References:

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