

ORIGINAL REPORT

Description of hypersensitivity adverse events following administration of heparin that was potentially contaminated with oversulfated chondroitin sulfate in early 2008[‡]

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SUMMARY

Purpose To characterize the nature of a heparin contaminant's clinical effects in cases reported to the Adverse Event Reporting System (AERS). The FDA received reports of heparin-associated adverse events (AEs) starting in late 2007–early 2008 during a national investigation of allergic-type events. The investigation identified Baxter Healthcare-brand heparin product due to its strongest association with the events. Later, oversulfated chondroitin sulfate (OSCS), a heparin-like contaminant, was discovered.

Methods This study was a case series of heparin reports in AERS received 1 January 2008 to 31 March 2008. Variables considered were frequency of treatment settings, AEs, mortality; as well as heparin dose and OSCS contamination.

Results Five hundred seventy-four AERS cases (unduplicated reports) were identified and included. Of 94 cases with a fatal outcome, 68 reported at least one AE term from the list used to identify an allergic-type event. Nearly 75% of AEs in cases of IV administration ($n = 170/233$) reportedly occurred within 10 minutes, whereas over half of subcutaneous administration cases ($n = 13/23$) resulted in times-to-event of greater than 24 hours. Although cases with a time-to-event of less than 10 minutes appeared to correlate with higher levels of OSCS contamination, no clear differences were noted between high- and low-to-absent OSCS concentration lots with respect to AEs observed.

Conclusions Intravenous administration and a higher OSCS concentration appeared to correlate with a more rapid onset of event. The FDA continues to monitor AEs associated with heparin use and has taken appropriate regulatory action to ensure a safe heparin drug supply. Published in 2010 by John Wiley & Sons, Ltd.

KEY WORDS — heparin; adverse events; contamination

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INTRODUCTION

On 7 January 2008, the Missouri Department of Health and Senior Services notified the Centers for Disease Control and Prevention (CDC) about a cluster of allergic-type events among hemodialysis patients at a

pediatric hospital. Symptoms occurred within minutes after the initiation of dialysis. Manifestations included facial edema, tachycardia, hypotension, urticaria, and nausea.¹ A facility-based case–control analysis² found that the use of Baxter heparin was most significantly associated with the presence of adverse events (AEs) at the facility, reported by all case facilities and only one control facility. Baxter Healthcare recalled nine lots of heparin³ in mid-January 2008, followed in late February 2008, by a recall of all multiple-dose and single-dose vials.⁴

Analysis of some vials of heparin manufactured by Baxter Healthcare from facilities that reported AEs

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revealed a substance identified as oversulfated chondroitin sulfate (OSCS).² OSCS is synthetically manufactured, mimics heparin's anticoagulant qualities and is a modified form of chondroitin sulfate which is a naturally occurring substance made from animal cartilage. *In vitro*, Kishimoto *et al.* demonstrated that OSCS found in contaminated heparin directly activated the kinin–kallikrein vasoactive mediator. OSCS-containing heparin and synthetically derived OSCS induced hypotension associated with kallikrein activation when administered by intravenous infusion in swine.⁵

In response to this outbreak, FDA developed and publically posted test methods for detecting the contaminant (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm112597.htm#screening>), initiated a sampling program to detect contaminated product as it reached U.S. borders, and increased the inspectional coverage of all heparin manufacturers. As a result of these efforts, FDA was able to place firms under Import Alert (automatic detention without physical examination) to prevent the entry of contaminated heparin into the U.S. In addition, FDA worked with the United States Pharmacopeia (USP) to include the enhanced test methods in the Heparin Sodium API monograph update of June 2008. FDA used the Adverse Event Reporting System (AERS), the largest passive surveillance system in the United States for drug AEs, to follow AEs that were reported in patients receiving heparin. Active surveillance tools that cover a large enough proportion of the US population, with procedures and protocols set up for an outbreak situation, were not available. In an effort to be transparent with the public, the FDA published on its website in early 2008 the numbers of reported deaths that occurred in patients that had been administered heparin. These numbers, while deduplicated, had not been assessed for causality. Therefore, many of the ill patients that received heparin and died from other causes were not figured into (subtracted from) the total counts. This was explained on the FDA website.

The purpose of this study was to describe associations, patterns, or signals among allergic-type heparin-associated AEs that may not have been apparent in the more circumscribed sample previously investigated.^{1,2}

METHODS

Review procedures

AERS is a surveillance system that receives voluntary reports on AEs after drug or biologic administration.⁶ We conducted a case series study and analyzed reports

of allergic-type events received by AERS between 1 January 2008 and 31 March 2008 with heparin identified as the suspect product. A case in this series is defined as an unduplicated report to AERS fulfilling the case definition as outlined below. In some instances there was scant demographic information, resulting in challenging comparisons for the purpose of deduplication. We selected for allergic-type events using the Medical Dictionary for Regulatory Activities (MedDRA) international terminology codes under the Standardized MedDRA Query anaphylactic reaction, which included 72 unique preferred terms, as well as additional preferred terms of interest (Appendix 1). At least two reviewers independently evaluated each case to abstract pertinent clinical data and to assess the relationship between heparin treatment and the reported events. Case follow-up information provided by the manufacturers [as per CFR 314.80(c)(1)(ii)] through 30 September 2008 was used to update the abstracted data elements and the heparin-event assessment. Active case follow-up by the authors was generally not performed. Cases were defined by the reporting of at least one of the following clinical events: angioedema; decreased blood pressure; adverse gastrointestinal events; inadequate coagulation; and adverse neurologic, respiratory, or skin events. Three cases did not report at least one of these clinical events but described manifestations of hypersensitivity (see Appendix 1) and were therefore included. The abstracted information from each of the two independent case reviews was compared to identify inter-observer discrepancies, which were subsequently reconciled by consensus of the original reviewers. Cases were excluded if they had a clear alternative clinical explanation, such as an event relationship with concomitant treatments, infections, or other co-morbid conditions; the case was not interpretable; the event took place before 1 January 2007; the diagnosis was heparin induced thrombocytopenia; if it was unclear whether the patient received heparin; or the case was from the literature. These exclusions were a matter of clinical judgment, and were adjudicated by two or more reviewers.

Heparin lot analysis

The FDA Division of Pharmaceutical Analysis, Office of Testing and Research, Office of Pharmaceutical Science used capillary electrophoresis^{7,8} for quantitating OSCS concentration using finished product samples. Of the seven lots evaluated, a second independent sample was only available for five lots. Evaluation of those samples using capillary electrophoresis and evaluation of samples from each lot using

SAX/HPLC (strong anion exchange liquid chromatography)⁹ led to similar results. Samples had been sent to the FDA or taken by FDA Inspectors from either manufacturing or healthcare delivery sites.

Lots were categorized as low-to-absent OSCS or higher OSCS, based on empiric cut-off points (see Results Section). Low-to-absent and higher concentrations of contaminant were dichotomized empirically based on the observed natural breakpoint of lower or higher than 5% OSCS.

When multiple lots were available at a facility and reported in a given case, we defined exposure to a higher concentration lot as the reporting of at least one higher concentration lot out of all lots reported; exposure to a low-to-absent concentration lot was defined as the reporting of low-to-absent concentration lots only. Cases that reported a low-to-absent concentration lot(s) in addition to lots of unknown concentration were not included in the OSCS analysis.

Descriptive analysis

Reports to AERS are classified as serious or non-serious according to U.S. regulations (21 CFR 314.80). We categorized the time intervals between the administration of heparin and onset of AEs as ≤ 10 minutes, > 10 minutes ≤ 1 hour, $1 \text{ hour} < 24$ hours, and ≥ 24 hours. Doses were standardized to patient weight and categorized into quartiles. We have not used statistical testing in our analysis because of the likely effect of the biases inherent to AERS.¹⁰ FDA made an effort to thoroughly investigate all AE data available in a timely fashion. FDA made an effort to thoroughly investigate all AE data available in a timely fashion. In early 2008, Baxter and APP, the firms with the largest heparin market share at that time, agreed to submit all AE reports on an expedited basis. It included reports normally not required to be submitted on an expedited basis (i.e., reports of serious, expected AEs and all non-serious AEs) in addition to those required to be submitted within 15 days (i.e., initial and follow-up reports of serious, unexpected AEs).

In a separate analysis, we assessed all fatal cases in which heparin was a suspect drug received by AERS over the time period of 1 January 2008–31 March 2008, regardless of the events reported. Assessment criteria included the temporal relationships between treatment, the AEs, and death, and the potential contributions that co-morbid disease or other drug products had with the events. The cases were reviewed by two reviewers blinded to each other's review, and were categorized as probable/likely, possible, unlikely attributable to heparin, or unable to assess according to an algorithm

that included important clinical features of the CDC case definition² (Appendix 2). Although some reports included medical records, in general the reports reviewed had no supplementary information besides what was in the report. Therefore, detailed information, for example, on patient comorbidities often was not available. This lack of relevant information was considered in our construction of appropriate assessment criteria.

RESULTS

Summary characteristics

A total of 771 reports of AEs were identified that reported at least one allergic-type event. After removal of duplicates and removal based on other criteria (Appendix 3), a final case series of 574 cases was identified (Appendix 3). Table 1 summarizes the characteristics of the 574 cases used for analysis. Note that the majority of the cases were reported by a health care professional. The percentage of missing data for key variables includes: Age – 18.5%, Sex – 7.7%, Route of administration – 17.1%, Final dose – 62.7%, Time-to-Event – 45.6%, and Lot number – 31.7%. Heparin from Baxter was the suspect drug in 432/465 (93%) of cases with known manufacturer information (Table 1), though Baxter supplied approximately half of the heparin to the US market during the time of these cases.¹¹

Adverse events

Figure 1 shows the number of cases that occurred and were reported by month. Five hundred sixty eight cases (99%) were reported to FDA after the first Baxter recall³ on 17 January 2008. Figure 2 shows monthly event date distributions of heparin SMQ+ (allergic-type) AERS reports received 1 January 2007 to 30 September 2008 with death reports and non-death reports separated on the graph and possible duplicates included. For approximately 8 months of 2007, there was a baseline reporting of allergic-type AEs after heparin therapy. Towards the end of 2007 there was a gradual increase in the number of monthly events followed by a rapid peak in December 2007 to January 2008, and a gradual decrease to baseline reporting from February to May 2008.

Table 2 shows the number and proportion of cases reporting at least one AE in each of seven categories, and the principal preferred terms within each category. The five most frequently reported terms included

Table 1. Demographics and characteristics of all cases ($n = 574$)

Demographic or characteristic	Observation
Age (years) n observations = 468	Median = 58 Mean = 57 Range = 2 – 97 Interquartile range = 45–70
Sex	Female = 277 (48%) Male = 253 (44%) Unknown = 44 (8%)
Clinical setting	Hemodialysis* = 194 (34%) Peritoneal dialysis = 109 (19%) Cardiac surgery [†] = 93 (16%) Prophylactic use other = 56 (10%) Photopheresis/Apheresis = 29 (5%) Treatment of thromboembolism = 27 (5%) Catheter maintenance = 22 (4%) Other = 13 (2%) Unknown = 31 (5%)
Medical history [‡]	Renal disease = 317 (55%) Cardiovascular disease = 256 (45%) Diabetes mellitus = 108 (19%) Respiratory disease = 35 (6%) Cancer = 30 (5%) Organ or bone marrow transplant = 23 (4%) Autoimmune disease = 17 (3%) Liver disease = 5 (1%)
Manufacturer of heparin used	Baxter Healthcare = 432 (75%) Abraxis/APP Pharmaceuticals = 23 (4%) Hospira = 5 (<1%) Other = 3 (<1%) B. Braun Medical = 2 (<1%) Unknown = 109 (19%)
Adverse event category based on case review	Decreased blood pressure = 300 (52%) Gastrointestinal = 284 (49%) Skin = 201 (35%) Respiratory = 132 (23%) Neurologic = 121 (21%) Angioedema = 54 (9%) Inadequate effect = 19 (3%)
Category of treatment for adverse events	Other clinical or medical interventions [§] = 122 (21%) Antihistamine = 81 (14%) IV fluid administration = 77 (13%) IV pressor agent = 47 (8%) Oxygen = 51 (9%) Systemic steroid = 27 (5%)
Regulatory outcome	Non-serious = 359 (63%) Hospitalization = 83 (14%) Death = 48 (8%) Life threatening = 45 (8%) Medically important = 28 (5%) Required intervention = 6 (1%) Disability = 5 (1%)
Reporter qualifications	Health care professional = 335 (58%) Patient or family member = 182 cases (32%) Attorney = 3 (<1%)

*Cases where the clinical setting was reported as “dialysis” are categorized as hemodialysis.

[†]Cases where the clinical setting was reported as “cardiac catheterization” are categorized as cardiac surgery.

[‡]Medical history was incompletely reported in many cases. An absence of reported medical history is not evidence of an absence of prior medical conditions.

[§]Other clinical or medical interventions included but were not limited to treatment with antibiotics, antiemetics, pain medications, subcutaneous epinephrine, management of the dialyzer and/or hemodialysis rates, or cardiopulmonary bypass.

^{||}Outcome as determined by the reporting manufacturer or the MedWatch reporter and categorized by 21 CFR 314.80.

ADVERSE EVENTS REPORTED FOLLOWING HEPARIN IN EARLY 2008

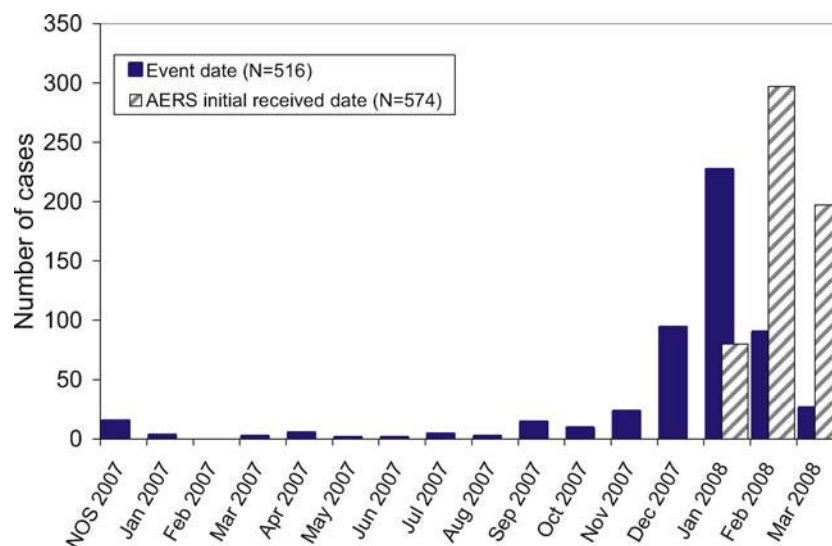


Figure 1. Allergic-type adverse event cases without duplicates received to AERS 1 January 2008–31 March 2008

nausea (192), hypotension (182), dyspnea (129), vomiting (120), and blood pressure decreased (111).

In the setting of peritoneal dialysis ($n = 109$), the time-to-event was unclear in most cases. Over 80% of patients

reported adverse GI events, such as nausea, vomiting, diarrhea, and abdominal pain. Although 39% of cases ($n = 42$) reported decreased blood pressure, 31 of the 42 did not provide objective data for such in the report.

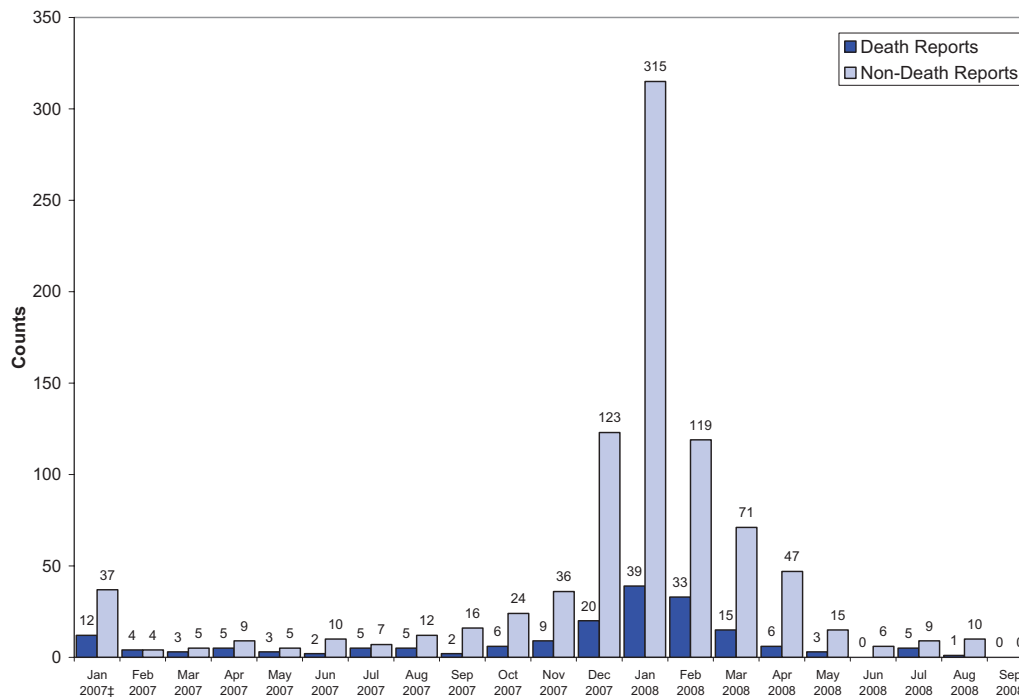


Figure 2. Monthly event date distributions of heparin SMQ+ (allergic-type) AERS reports received 1 January 2007 to 30 September 2008. Figures in the chart are unreviewed reports; duplicate reports have not been identified and removed. Not all of the reports have been reviewed to assess the nature of the event or to determine if a causal relationship exists between the adverse event and the drug product ($n = 1254$ reports identified with event dates provided in 1117 reports). Reports with event dates prior to 1 January 2007 are not shown. The apparent spike of reports in January 2007 is an AERS artifact related to events that are specified only to the calendar year being assigned to January of that year

Table 2. Number of cases and the most frequently reported MedDRA preferred terms by adverse event category*

Adverse event category	MedDRA preferred term	No. of cases
Decreased blood pressure		300 (52.3%)
	Hypotension	182
	Blood pressure decreased	111
Gastrointestinal		284 (49.5%)
	Nausea	192
	Vomiting	120
	Diarrhea	66
	Abdominal pain	62
	Abdominal pain upper	53
Skin		201 (35.0%)
	Flushing	64
	Hyperhidrosis	51
	Burning sensation	25
	Feeling hot	24
	Pruritus	21
Respiratory		132 (23.0%)
	Dyspnea	129
	Cough	7
Neurologic		121 (21.1%)
	Dizziness	94
	Unresponsive to stimuli	25
	Loss of consciousness	23
	Paraesthesia oral	21
	Paraesthesia	19
Angioedema		54 (9.4%)
	Pharyngeal edema	13
	Swelling face	11
	Lip swelling	9
	Swollen tongue	7
	Urticaria	7
Inadequate effect		19 (3.3%)
	Coagulation time shortened	11
	Drug ineffective	4

*Cases may have reported more than one preferred term in a given category. The top two to five reported preferred terms are noted for each category.

Temporal associations with dose and administration route

The route of heparin administration was reported in 476 cases. The three most frequently reported administration methods included intravenous use in 318 cases (66.8% of 476 cases), peritoneal dialysate exchange in 103 cases (21.6%), and subcutaneous administration in 49 cases (10.3%). Two hundred fifty-six cases reported the time-to-event for either intravenous or subcutaneous use. Nearly 75% of AEs in cases of IV administration ($n = 170/233$) reportedly occurred within 10 minutes (Appendix 4), whereas over half of subcutaneous administration cases ($n = 13/23$) resulted in times to event of greater than 24 hours (Appendix 4).

OSCS-contamination level and adverse events

There were 392 cases (68.3% of 574 cases) that had at least one heparin lot reported. Many cases reported

multiple product lot numbers without further indicating which lot(s) was specifically administered to the patient. The 10 most frequently reported lots accounted for 254 of the 574 (44.3%) cases in the series. Among the 10 lots, only 7 were available to the FDA and were tested for the concentration of the OSCS contaminant. These 7 lots accounted for 223 cases (38.9% of 574). The results of initial lot testing for OSCS by capillary electrophoresis were 0, 2.6, 9.5, 12, 16.4, 21.7, and 23.5% OSCS for these 7 lots. Low-to-absent and higher concentrations of contaminant were dichotomized based on a natural breakpoint of lower or higher than 5% OSCS (Appendix 5). No *a priori* determination of the cut off between the two levels of exposure was made. The dichotomization was done in an attempt to examine the potential dose–effect relationship between the contamination level and the adverse reactions. There was some variation between vials when two vials were tested from the same lot. This variation noted was from 9% to 26% of the initial vial tested and did not result in differences in the assignment to high or low groupings. The variation seen may be due to assay variability as well as differences between vials from the same lots. In five of the seven lots, an additional capillary electrophoresis determination was performed; and the results agreed with the assignment of lots to low-to-absent and higher concentration of OSCS. All seven lots were also tested by SAX/HPLC.⁸ We obtained the same natural breakpoint of lower and higher OSCS lots. The two lots with low-to-absent contamination ranged from 0% to 3.5%; while the five lots with higher contamination ranged from 10.4% to 27.4% OSCS, and 35 of 223 cases (15.7%) reported the use of a low-to-absent concentration lot only, whereas 184 cases (82.5%) reported the use of at least one higher concentration lot.

The proportions of AEs were approximately the same in the low-to-absent as higher concentration OSCS lots (Table 3). Cases with a time-to-event of less than 10 minutes appeared to correlate with higher levels of OSCS contamination. Of 105 cases of intravenous administration that reported a time-to-event of less than 10 minutes, 102 (97.1%) reported at least one higher concentration lot (Figure 3); whereas of 27 cases of intravenous administration that reported a time-to-event of longer than 10 minutes, 19 (70.4%) reported at least one higher concentration lot.

Mortality

Of 94 cases with a fatal outcome, 68 reported at least one AE term from the list used to identify an allergic-

Table 3. Proportion of cases reporting low-to-absent and higher* OSCS-concentration heparin lots by adverse event category

Adverse event category	% of cases reporting low-to-absent OSCS lots (<i>n</i> = 35)	% of cases reporting higher* OSCS lots (<i>n</i> = 184)
Decreased blood pressure	48.6	61.4
Gastrointestinal	74.3	50.5
Skin	25.7	33.2
Respiratory	25.7	28.8
Neurologic	20.0	27.7
Angioedema	8.6	12.0

*Cases reported at least one higher concentration lot and may or may not have reported additional lower concentration lots or lots with an unknown concentration.

type event (Appendix 1). We assessed three deaths as having a probable/likely association and six deaths with a possible association with heparin therapy. The three probable/likely association patients were all cardiology patients: an 80-year-old undergoing cardiac catheterization, a 30-year-old undergoing mitral valve replacement, and a 73-year-old undergoing coronary artery bypass for coronary artery occlusion. Lot numbers were not reported in these three cases assessed as probable/likely. Product lot numbers were reported in two of the six possible cases. In 85 of the 94 cases, we assessed the strength of association between heparin treatment and the patient's death as unlikely (*n* = 41) or not assessable (*n* = 44).

The case series of 68 reports that contained an AE term associated with an allergic-type event had a median age of 72 years and were more male (59%) than female (41%). Fifteen of 68 reports (22%) contained information on the time from heparin administration to onset of event; 11 cases reported a time-to-onset within 1 hour of heparin administration. The most frequently

reported AE categories were decreased blood pressure (59%), gastrointestinal (40%), and respiratory (37%). For the gastrointestinal category, the most commonly reported events were nausea, vomiting, diarrhea and abdominal pain. The most commonly reported event in the respiratory category was dyspnea. The cause of death was reported in about half of the reports. The most frequently reported causes were cardiac (9), hypotension (7), hemorrhage (4), thrombosis (4), and sepsis (4). Dosing information was available for only 8/68 cases. Four of 24 deaths associated with an allergic-type event and assessed to have an unlikely association with heparin had a reported time-to-onset (15 minutes, same day, 4 days and 7 days). There were therefore insufficient numbers for further assessment of the time-to-onset variable in the unlikely cases.

DISCUSSION

This study describes 574 cases reported to AERS and selected for symptoms of an allergic type AE that potentially could be related to OSCS contamination during a time period when OSCS contamination was detected in the heparin source. The quality of information in the reports was variable, with many case reports lacking basic or critical clinical information. This feature limited the ability to make firm conclusions about the role of heparin in the development of the reported AEs.

The majority of events occurred within the first 10 minutes after heparin administration. Even though we have a very limited number of cases in each subgroup, cases with a time-to-event of less than 10 minutes appeared to correlate with higher levels of OSCS contamination. No clear trends in association between the OSCS concentration and AE categories were noted. Possible reasons for the lack of trends in association of OSCS concentration and AEs include small numbers of lots tested, small numbers of AE cases in the study, and the fact that the data are from a passive surveillance system with underreporting, inconsistent reporting, and reporting which lacks essential details. Also, no reasonable denominator is available since both inpatient and outpatient use are represented herein, and detailed knowledge of heparin usage patterns throughout the United States is not available to these authors.

There was limited inferential value in the passive surveillance data regarding deaths and OSCS contamination. The cause of death was reported in about half of the 94 fatal cases. The most frequently reported causes were hypotension or cardiac reasons. There were substantial confounding factors in most cases that precluded making a determination that a death was

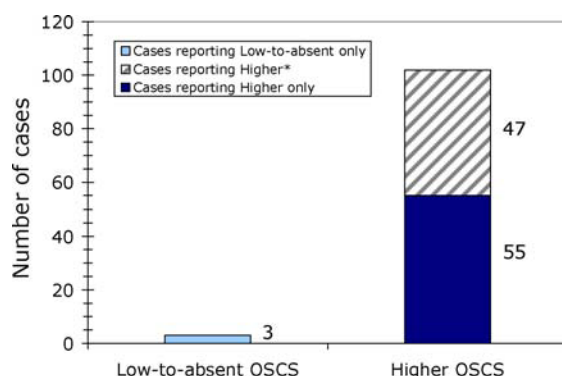


Figure 3. Number of cases of intravenous administration reporting time-to-event < 10 minutes for Low-to-absent OSCS concentration lots (*n* = 3) and Higher OSCS concentration lots (*n* = 105). *Cases where multiple lots were available at the facility and reported to a given case. Exposure to a higher concentration lot in these cases is defined as the reporting of at least one higher concentration lot out of all lots reported

causally related to heparin. In the three cases assessed as having a probable/likely association with heparin, the lack of certain clinical details, the presence of comorbid conditions, and the lack of lot information made it difficult to conclude definitively that OSCS-contaminated heparin played a role in the events and outcomes reported. These estimates may include underreporting, though they were performed during a period of stimulated reporting, as mentioned below.

Though some had postulated that “effectiveness”¹² of heparin and heparin-induced thrombocytopenia (HIT)¹³ might have been impacted during this crisis, this case series was not constructed to measure these two AEs. In fact, HIT was systematically excluded from this study, and the number of “lack of effect” reports (Table 2) almost certainly does not represent the number of this AE for this product since this AE was not part of the search criteria.

A small number of AEs reported in this series occurred in the first 8 months of 2007, suggesting a low background rate of allergic-type events in patients receiving heparin. Of note, anaphylactic and other allergic-type events are listed in the approved labeling of heparin. Few reports were submitted to the drug manufacturers or FDA until after the public and medical communities were made aware of the heparin recall issued by Baxter Healthcare. This is consistent with the well-known phenomenon of stimulated reporting.¹⁴ The majority of cases described AEs that were non-serious. Had FDA not made an arrangement with Baxter to receive non-serious reports in an expedited fashion, the overall number of cases would have been lower. The CDC case-control study established the relationship between heparin and the adverse outcomes. Establishing this relationship with AERS data alone would have been challenging. Because the FDA did not have access to an active surveillance system with real-time information on heparin and AEs, AERS was the system used to monitor those events both in real-time, and also retrospectively, as in this analysis.

The lot analysis of the AERS data was based on low-to-absent (0–2.6%) and higher (9.5–23.5%) levels of OSCS contamination. This grouping was based on the available lot data and the limited numbers of cases. As difficult as it may be to assess differences, or lack of them, without statistical testing (which would be inappropriate in this study, see Methods Section), it appears there was no discernable difference between the clinical outcomes in the persons who had received low-to-absent lots and those who had received lots with high level of OSCS contamination. Possible reasons for this include the nature of data from a passive surveillance database,

the limited numbers in this study, and the nonlinear dose-response of OSCS activation of kallikrein.⁵

The uncertainty over the dose-response suggests there is no clear safe threshold for OSCS exposure based on these studies. The difference between low-to-absent and high OSCS levels in AERS data cannot be extrapolated to define a safe level of exposure threshold due to multiple factors. Although both the CDC study² and AERS cases show possible association between events and OSCS contamination, neither assesses the frequency of contaminated lots in unaffected patients.

As stated above, the Baxter heparin recall³ may have resulted in stimulated or biased reporting, but the recall would not have any impact on higher versus low-to-absent OSCS lots (both types of lots were included in the initial recall). In addition, the mechanism of OSCS kallikrein activation⁵ fits the observed events and thus provides biological plausibility¹⁵ to OSCS mediated AEs. Finally, the screening of heparin lots for OSCS correlated with a significant reduction of AEs by May 2008 (Figure 2).

CONCLUSION

This review summarizes the findings of the outbreak of allergic-type events associated with heparin for AERS reports received in the first quarter of 2008. The major findings follow:

- There was a low-level background of allergic or allergic-type AE cases in AERS for heparin in 2007 prior to the outbreak.
- Ninety-nine percent of cases were submitted to FDA MedWatch after the public announcement of the heparin recall, suggesting stimulated reporting.
- The majority of cases described AEs that were not serious (defined by regulation).
- Lots with higher concentration of OSCS appeared to be associated with a time-to-event of 10 minutes or less in selected cases with information on lot and OSCS concentration.
- In most death reports, there were substantial confounding factors that precluded making a determination that death was either possibly or probably related to heparin or that OSCS-contaminated heparin that had a causative role in cases assessed as probably related to heparin.

RECOMMENDATIONS

The FDA continues to monitor AEs associated with heparin use and has taken appropriate regulatory action related to ensuring a safe heparin drug supply.

The FDA is pursuing development of active surveillance that will have the ability to detect possible

adverse effects from medical products with consistent accurate documentation of medical effects.¹⁶

CONFLICT OF INTEREST STATEMENT

This study was sponsored by the United States Food and Drug Administration (USFDA), and included analysis of some spontaneous reports provided by companies with a vested interest in the product being studied. The companies supply the data to the USFDA because they have a regulatory obligation to do so. All authors of this manuscript worked for the USFDA when this study was performed, and do not have any financial conflicts of interest to disclose. The views expressed in this manuscript represent the opinions of the authors, and do not necessarily represent the views of the USFDA.

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KEY POINTS

- This study documents stimulated reporting of heparin-related events to the Adverse Event Reporting System in early 2008.
- Intravenous administration and a higher OPCS concentration appeared to correlate with a more rapid onset of event after heparin administration.

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APPENDIX 1

Anaphylactic reaction SMQ and non-SMQ preferred terms (PTs) used for AERS search

Scope category	Preferred terms
SMQ Narrow	Anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, circulatory collapse, shock, type I hypersensitivity
SMQ Broad Oral-Respiratory PTs	Acute respiratory failure, asthma, bronchial edema, bronchospasm, cardio-respiratory distress, chest discomfort, choking, choking sensation, cough, dyspnea, hyperventilation, laryngeal dyspnea, laryngeal edema, laryngospasm, laryngotracheal edema, edema mouth, oropharyngeal spasm, oropharyngeal swelling, respiratory arrest, respiratory distress, respiratory failure, reversible airways obstruction, sensation of foreign body, sneezing, stridor, swollen tongue, throat tightness, tongue edema, tracheal obstruction, tracheal edema, wheezing
SMQ Broad Skin PTs	Allergic edema, angioedema, erythema, eye edema, eye swelling, eyelid edema, face edema, fixed eruption, flushing, generalized erythema, lip edema, lip swelling, edema, periorbital edema, pruritus, pruritus allergic, pruritus generalized, rash, rash erythematous, rash generalized, rash pruritic, skin swelling, swelling, swelling face, urticaria, urticaria papular
SMQ Broad Cardiovascular PTs	Blood pressure decreased, blood pressure diastolic decreased, blood pressure systolic decreased, cardiac arrest, cardio-respiratory arrest, cardiovascular insufficiency, diastolic hypotension, hypotension
Non-SMQ PTs of interest	Diarrhea, drug hypersensitivity, hyperhidrosis, hypersensitivity, loss of consciousness, nausea, vomiting

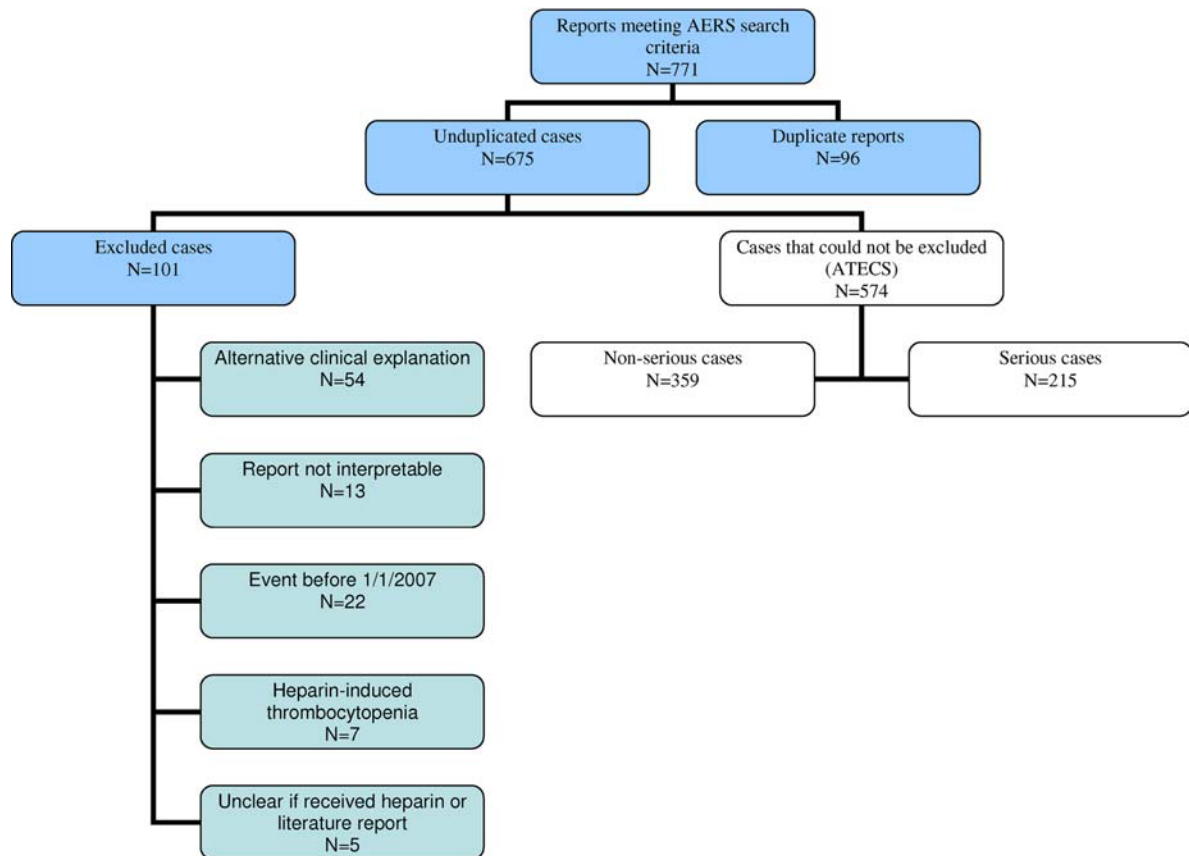
APPENDIX 2

Death association categories and criteria

Association	Assessment criteria
Probable/Likely	Adverse event had reasonable time relationship to heparin administration (minutes to ≤ 1 hour) AND Death unlikely related to disease or other drug products AND Death occurred during adverse event or within hours of heparin administration
Possible	Adverse event had reasonable time relationship to heparin administration (minutes to ≤ 1 hour) AND Possible contributory role of disease or other drug products (another possible explanation for the event)
Unlikely	Event had an improbable time relationship (> 1 hour) to heparin administration OR Disease or other drug products provide plausible explanations (more likely explanation for the event than heparin administration)
Unable to assess	Cannot be assessed due to insufficient or contradictory information

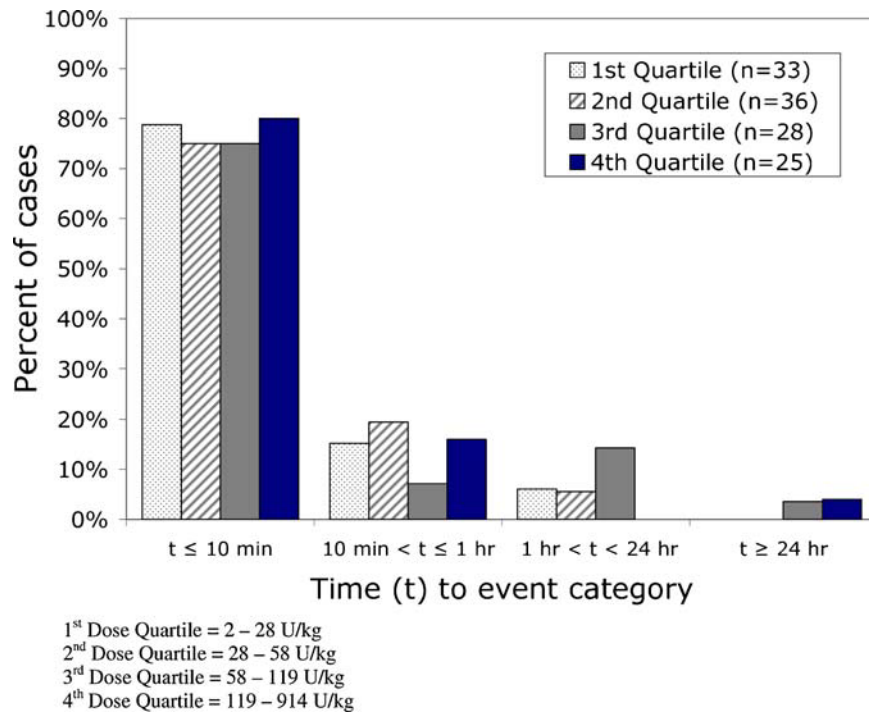
APPENDIX 3

Summary of case series development.



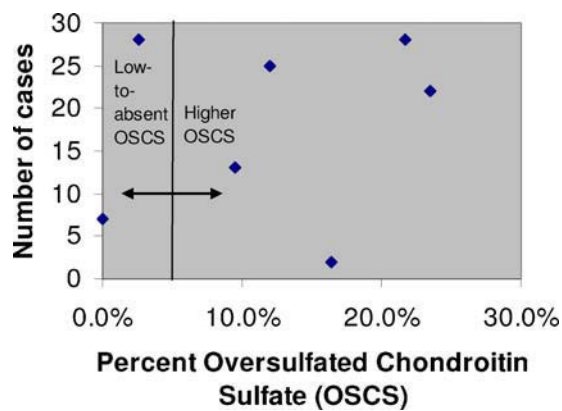
APPENDIX 4

Percent of cases of intravenous administration in each dose quartile categorized by time to event



APPENDIX 5

Percent oversulfated chondroitin sulfate in lots administered to cases in the heparin case series*.



APPENDIX 6

Demographics and characteristics of fatal cases reporting at least one PT from the AERS search method ($n = 68$)

Demographic or characteristic		Observation
Age (years)		Median = 72
n observations = 61		Range = 27–91
Sex		Male = 40 (59%) Female = 28 (41%)
Clinical setting		Cardiac surgery* = 20 (29%) Hemodialysis = 16 (24%) Peritoneal dialysis = 8 (12%) Prophylactic use other = 7 (10%) Treatment of thromboembolism = 5 (7%) Other = 2 (3%) Catheter maintenance = 1 (2%) Unknown = 9 (13%)
Adverse event category		Decreased blood pressure = 40 (59%) Gastrointestinal = 27 (40%) Respiratory = 25 (37%) Cardiac arrest = 16 (24%) Neurologic = 14 (21%) Hemorrhagic = 13 (19%) Skin = 7 (10%) Angioedema = 3 (4%) Inadequate effect = 2 (3%)
Time from heparin administration to event [†]		≤10 minutes = 4 (6%) ≤1 hour = 7 (10%) ≤24 hours = 2 (3%) >24 hours = 2 (3%) Unknown = 53 (78%)
Time from heparin administration to death [†]		≤1 day = 8 (12%) ≤1 week = 8 (12%) >1 week = 8 (12%) Unknown = 44 (64%)
Reported cause of death		Cardiac = 9 Hypotension [‡] = 7 Hemorrhage = 4 Thrombosis = 4 Sepsis = 4 Renal failure = 2 Pneumonia = 2 Multi-organ failure = 2 Respiratory failure = 1 Allergic symptoms = 1 Unknown = 32
Death association category		Probable/likely = 3 (4%) Possible = 6 (9%) Unlikely = 24 (35%) Unassessable = 35 (52%)
Manufacturer of heparin used, n observations = 28		Baxter Healthcare = 21 Abraxis/APP Pharmaceuticals = 3 Hospira = 2 Amsino = 1 Abraxis/APP and Baxter = 1
Reporter's qualifications		Consumer = 42 (62%) Healthcare professional = 22 (32%) Lawyer = 2 (3%) Unknown = 2 (3%)

*Cases where the clinical setting was reported as cardiac catheterization were categorized as cardiac surgery.

[†]Time categories are mutually exclusive.

[‡]Two cases reported additional causes of death – renal failure in one case and heart failure in a second case.