Incidence of Heparin-Induced Thrombocytopenia and "Argatroban" Dollars At University Hospital In The United States

Peer review status:
No

Corresponding Author:
Dr. Deepak Gupta,
Anesthesiologist, Wayne State University, 48201 - United States of America

Submitting Author:
Dr. Deepak Gupta,
Anesthesiologist, Wayne State University, 48201 - United States of America

Other Authors:
Dr. Farhad Ghoddoussi,
Research Associate, Anesthesiology, Wayne State University - United States of America
Dr. Vinay Pallekonda,
Assistant Professor, Anesthesiology/Critical Care, Wayne State University/Detroit Medical Center - United States of America

Article ID: WMC005444
Article Type: Original Articles
Article URL: http://www.webmedcentral.com/article_view/5444
Subject Categories: HAEMATOLOGY
Keywords: heparin-induced thrombocytopenia, argatroban, platelet factor 4 antibody, serotonin release assay, incidence, healthcare costs

How to cite the article: Gupta D, Ghoddoussi F, Pallekonda V. Incidence of Heparin-Induced Thrombocytopenia and "Argatroban" Dollars At University Hospital In The United States. WebmedCentral HAEMATOLOGY 2018;9(4):WMC005444

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC-BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Source(s) of Funding:
NONE

Competing Interests:
NONE
Incidence of Heparin-Induced Thrombocytopenia and "Argatroban" Dollars At University Hospital In The United States

Author(s): Gupta D, Ghoddoussi F, Pallekonda V

Abstract

Background: According to published medical literature, there is variable incidence of heparin-induced thrombocytopenia (HIT), a life-threatening pro-thrombotic state, complicating unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) use with immunogenic activation cascade evolving into arteriovenous thromboembolism.

Objective: To quantify incidence of suspected and/or confirmed HIT at our university hospital in the United States (US).

Materials and Methods: Presuming suspected/confirmed HIT whenever argatroban was used during the five year period (2009-2013), the argatroban usage patient lists were tabulated through our institutional pharmacy database. Subsequently, all these patients’ electronic medical records were accessed to tabulate the final list of those patients wherein the presence of platelet factor 4 antibodies (PF4A) were tested based on the suspicion of HIT, and/or serotonin release assay (SRA) was used to further confirm HIT among patients with positively present PF4A. Simultaneously, the overall usage of UFH and LMWH at our hospital were assessed through our institutional pharmacy database to provide the denominator for calculating the incidence of HIT in our university hospital during the five year period.

Results: Over a five-year period (2009-2013), UFH and/or LMWH were administered to patients during 64,250 unique admissions while argatroban was administered to patients during 90 unique admissions over the same period. Among those 90 admissions, patients were tested for suspected HIT during 64 admissions only wherein presence of PF4A presumptively confirmed incidence of HIT during 18 admissions only. Only two patients were truly confirmed as SRA-positive HIT patients with one of them expiring during the hospital stay (50% mortality). During 64 admissions where HIT was suspected, the total argatroban costs incurred by the hospital was 142,809 US Dollars and the total argatroban charges levied on the patients/third-party-payers was 1,183,669 US Dollars.

Conclusions: The presumed incidence of HIT based on PF4A confirmation was at least 2 admissions among every 10,000 admissions receiving UFH and/or LMWH while the true incidence of HIT based on SRA positivity was at least 3 admissions among every 100,000 admissions receiving UFH and/or LMWH. Each admission during the five-year period where UFH and/or LMWH was used had an additional hospital cost of at least 2.22 "argatroban" US Dollars with patient/third-party-payer charge of at least 18.42 "argatroban" US Dollars as a reflection of our institutional economic burden secondary to suspected/confirmed HIT among our patient admissions.

Introduction

Heparin-induced thrombocytopenia (HIT), a life-threatening pro-thrombotic state, complicates unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) use when immunogenic activation cascade evolves into arteriovenous thromboembolism. Incidence of HIT varies per available medical literature. Therefore it is worthwhile to investigate local incidence of HIT at our university hospital to quantify (a) if HIT had been overzealously suspected among our hospital admissions with correspondingly costly argatroban treatment for both presumed and confirmed HIT to avoid HIT-related life-threatening arterial thromboembolic phenomena, or (b) if suspicion of HIT and subsequent confirmation of HIT utilizing testing for platelet factor 4 antibodies (PF4A) and/or serotonin release assay (SRA) had been an under-utilized phenomena at our university hospital as compared to documented historical variable incidence of suspected/confirmed HIT in published medical literature. Essentially, the primary objective of our retrospective review was to quantify incidence of suspected and/or confirmed HIT at our university hospital in the United States (US).

Methods

After Institutional Review Board approval for
practitioners had non-HIT indications for using argatroban or because their already known allergic to heparin thus warranting the tested for PF4A either because these patients were reviewed if the remaining 26 admissions did NOT get of HIT during 18 admissions only. It was NOT presence of PF4A subsequently confirmed incidence during 64 admissions only wherein the presence of PF4A were tested based on the suspicion of HIT, and/or SRA was used to further confirm HIT among patients with positively present PF4A. The final enlisted patient charts were reviewed for the following: age, sex, ethnicity, body mass index, platelet counts, incidence of thrombotic events, duration of hospital stay, complications and total costs of argatroban used. Simultaneously, the overall usage of UFH and LMWH at our hospital were assessed through our institutional pharmacy database to provide the denominator for calculating the incidence of HIT in our university hospital during the five year period.

Statistical Analysis

The incidence was analyzed in terms of how often HIT was happening every 10,000 patient admissions receiving UFH and/or LMWH at our university hospital over the five year period. As for suspected HIT patients vs. confirmed HIT patients, ANOVA (Analysis of Variance) compared the continuous data while Fisher Exact Test compared categorical data with p value < 0.05 being statistically significant.

Results

Over a five-year period (2009-2013), UFH and/or LMWH were administered to patients during 64,250 unique admissions (Table 1) to our university hospital while argatroban was administered to patients during 90 unique admissions over the same period. Among those 90 admissions, patients were tested for suspected HIT during 64 admissions only wherein presence of PF4A subsequently confirmed incidence of HIT during 18 admissions only. It was NOT reviewed if the remaining 26 admissions did NOT get tested for PF4A either because these patients were already known allergic to heparin thus warranting the administration of argatroban or because their practitioners had non-HIT indications for using argatroban in them. Although we reviewed data based on argatroban use only and presumed suspected HIT-management protocols based on other medications like lepirudin to be extremely rare, the use of other HIT-management protocols could NOT be considered as non-existent. Therefore, our data deciphered that HIT was happening in at least 2 admissions among every 10,000 admissions receiving UFH and/or LMWH at our university hospital during 2009-2013. Moreover, HIT was happening in at least 4-7 admissions among every 10,000 admissions receiving UFH and/or LMWH during 2012-2013 because, according to our five-period review, 79% of all argatroban use was utilized during 2012-2013 period. Further review of the comparative data (Table 2) between patients who tested negative for PF4A vs. patients who tested positive for PF4A (presumed confirmation of HIT), the patients with confirmed HIT had (a) stayed significantly longer in the hospital after the suspicion for HIT had been raised, (b) significantly higher platelet counts at the time of discharge, (c) significantly higher likelihood to have heparin documented as allergy in their electronic medical records, and (d) correspondingly significant higher hospital costs (and patient charges) secondary to expected prolonged use of argatroban for confirmed HIT. Interestingly, during 64 admissions where HIT was suspected, the total argatroban costs incurred by the hospital was 142,809 US Dollars and the total “argatroban” US Dollars as a reflection of our local economic burden secondary to suspected/confirmed HIT among our patient admissions.

Although statistically insignificant, a clinically significant higher likelihood of new onset thrombosis and yet lower likelihood of palliation/expiration among HIT patients was observed suggesting that non-HIT etiology of thrombocytopenia may be more fatally catastrophic in critically ill patients even in the absence of new-onset thrombocytopenia; proactively suspecting/confirming HIT with early initiation of preemptive treatment by argatroban might have contributed to better outcomes among HIT patients as compared to critically ill patients with unclear treatment for thrombocytopenia of non-HIT origin. Additionally, the more likelihood of
thrombocytopenic patients' expiration with non-HIT etiology may also explain the shorter hospital "stay" of these non-HIT patients as compared to prolonged stay for therapeutically manageable confirmed HIT patients.

Interestingly, among 46 PF4A-negative patients, one out of the ten patients, who were tested with SRA too, had positive SRA after PF4A being negative initially, while among 18 PF4A-positive patients (presumed confirmation of HIT), only one out of the ten patients, who were tested with SRA, had positive SRA. When assuming that these two patients were the only truly confirmed HIT patients with one of them expiring during the hospital stay (50% mortality), the "true" incidence of HIT among our reviewed patients can be deemed as at least 3 admissions among every 100,000 admissions receiving UFH and/or LMWH at our university hospital during 2009-2013. However, as SRA has been a send-out test from our hospital to external laboratories wherein test results' return times have been approximately seven days, early "true" confirmation of HIT among our patients might have been impossible and therefore, based on clinical teams' judgments, all of our presumptively confirmed HIT patients with PF4A-positivity might have been treated with argatroban, as similar to average 6-days long therapeutic argatroban regimen documented by Aljabri et al (2016)1.

One thing to note is that the PF4A-positivity on screening is re-confirmed locally within our hospital by adding heparin to the tested samples to confirm platelet activation/aggregation, irrespective of clinical teams' decision for-or-against sending out SRA test. Additionally, the variability in documented heparin allergy in electronic medical records unravels a potential heterogeneity pointing out to following scenarios: (a) Patient had history of heparin allergy but PF4A was negative during the reviewed admission as PF4A from prior episode of HIT must have disappeared within 50-85 days8; (b) Patient developed heparin allergy in one of the future admissions following the reviewed admission; (c) Practitioner adjudged PF4A positivity as inconclusive in the absence of serotonin release assay positivity; (d) Patient had expired before heparin could be added as allergy into the electronic medical records. During the concise non-comprehensive review of patients' electronic medical records, it was not clear if HIT Pre-Test Scoring System's Score8 was documented before initiation of argatroban or if bleeding due to argatroban was the reason for cessation of argatroban rather than just ruled out HIT in patients with absent PF4A.

Discussion

Paradoxical thromboembolic phenomena1-10 with exposure to anticoagulant and antithrombotic heparin11 presenting initially as HIT can be catastrophic. Therefore, HIT warrants appropriate workup and diagnosis, with preemptive management (discontinuation of UFH/LMWH and addition of direct thrombin inhibitor like argatroban) in the interim while waiting for confirmation for PF4A presence and therapeutic management with direct thrombin inhibitors once PF4A presence has been confirmed. It is interesting to note that, after HIT Pre-Test Scoring System's Score prompts the testing for PF4A screening followed by PF4A confirmation by in-vitro heparin-challenge or by SRA test, PF4A lasts for only median 50-85 days8 and PF4A reappearance is not compulsory as a rule during repeat in-vivo heparin-exposure after their disappearance. However, heparin may get added to patients' electronic medical records as an allergy at the time of confirmed HIT and thereafter, the re-exposure to UFH/LMWH usually never happens after confirmed HIT/PF4A positivity. Henceforth, it may be difficult to examine the incidence of second, third and so forth episodes of HIT in the patients with known history of confirmed first episode of HIT.∴ ∴ ∴

Among 24,068 patient admissions with estimated exposure to UFH during 1-year retrospective study period (2003-2004), Smythe et al (2007)3 deduced incidence of HIT as 0.2%, meaning 20 admissions among every 10,000 patient admissions exposed to UFH. Comparatively, per our results, incidence of HIT was at least 2 admissions among every 10,000 admissions receiving UFH and/or LMWH during 5-year period (2009-2013; n=64250) to at least 4-7 admissions among every 10,000 admissions receiving UFH and/or LMWH during 2-year period (2012-2013; n=29516).

According to Cochrane database review by Junqueira et al (2017)12, as compared to UFH exposure, LMWH exposure is less likely to be complicated by HIT with or without new-onset thrombosis; however, in our retrospective review, our materials and methods were NOT deciphering if there was any difference in overall incidence of HIT between UFH-exposed patient admissions vs. LMWH-exposed patient admissions. Although Seigerman et al (2014)4 reported 0.3%
incidence of HIT among cardiac surgery patients nationwide in US hospitals (n=186,771). Kotwal et al (2014)\(^5\) reported 5.6% incidence of HIT and 0.8% incidence of HIT with thrombosis among cardiac surgery patients at single-center in India (n=125), and Wang et al (2013)\(^6\) reported 15% incidence of HIT and 2.5% incidence of HIT with thrombosis among vascular surgery patients at single-center in China (n=240), our single-center retrospective review with small number of patients (n=64) did NOT explore for evidence of higher incidence (if any) of confirmed HIT in cardiac surgery patients or vascular surgery patients. Â

Â Just like Greinacher et al (2005)\(^3\), 67% of our confirmed HIT patients were 60 years or more old. Among 882 confirmed HIT patients who were part of a multicenter study during 4-year period (1995-1998), Lewis et al (2006)\(^4\) reported thrombosis development risk being significantly higher among non-white patients (twice more likely than white patients) and among female patients (1.7 times more likely than male patients). Comparatively, among our very small group of HIT patients (n=18), 45% African-American patients and 43% Caucasian patients developed thrombosis; and similarly 45% female patients and 43% male patients developed thrombosis.

Â In a cohort of confirmed HIT among 62 patients over a 14-year retrospective study period, Warkeintin and Kelton (1996)\(^5\) demonstrated >50% risk of developing thrombosis within 30-days irrespective of the use of warfarin, the primary treatment modality for confirmed HIT during the study period other than just discontinuation of heparin. Even though we reviewed suspected/confirmed HIT patients managed with argatroban only, the development of new thrombosis in our patients during 5-year retrospective study period was still high (44%) despite the number of confirmed HIT patients being small (n=18).

Â Among 108 confirmed HIT patients during 4-year period (1991-1994), Nand et al (1997)\(^6\) reported 30% HIT patients developing new thrombosis, and consequently among patients with new thrombosis, 16% patients expired, 9% patients lost limbs and 9% patients stroked. Comparatively, among 18 confirmed HIT patients during our 5-year period (2009-2013), 44% HIT patients developed new thrombosis, and consequently among patients with new thrombosis, 38% patients expired or were transferred to palliation/hospice. Â

Â In regards to pharmacoeconomics concerns, Aljabri et al (2016)\(^7\) reported that, although argatroban is better with it being short-lasting (no cumulative effect) and eliminated via liver (no dose adjustment for kidney function), argatroban (1250 US Dollars) was costlier than fondaparinux (151 US Dollars) for HIT management according to one institution (Banner-University Medical Center, Tucson, Arizona) based costs estimate model; and when average wholesale price across the US was used for costs estimate model, argatroban (3081 US Dollars) was even costlier than bivalirudin (2187 US Dollars) for HIT management. Comparatively, per our results, average argatroban costs to our hospital for managing suspected/confirmed HIT (n=64) was 2231 US Dollars while average argatroban charges billed to suspected/confirmed HIT patients/third-party-payers was 18,495 US Dollars. Â

Â Our study has few limitations. Firstly, as it was a retrospective review logistically designed to be based only on argatroban usage, it might have underreported the incidence of HIT at our institution wherein it might have been possible that over the five-year period, the heterogeneity of the clinical practice might have varied from only discontinuation of UFH/LMWH in suspected HIT patients to therapeutic regimens with lepirudin or fondaparinux as alternatives to argatroban in confirmed HIT patients. Secondly, the potential for heterogeneity in ordering tests for PF4A in suspected HIT might have resulted in under-diagnosis and the potential for heterogeneity in ordering tests for SRA to reconfirm after PF4A positivity might have resulted in over-treatment for HIT. The send-out SRA test with test results' return times being so long did NOT help either as the patients might have been treated for a week or so as HIT until SRA test results excluded HIT. After PF4A screening positivity, the differences between local institutional confirmation of PF4A with heparin challenge vs. external laboratory confirmation of HIT with SRA highlighted the needs for SRA to be performed in-house in the university hospitals with large numbers of patient admissions who all would be exposed to UFH/LMWH. Although clinical teams' judgments' heterogeneity might have been based on HIT Pre-Test Scoring System's Score, our concise non-comprehensive review could NOT decipher their documentation in patients' electronic medical records and thus could NOT infer with confidence that heterogeneity in clinical practice in regards to ordering the laboratory tests and preemptively or therapeutically treating for suspected/confirmed HIT...
was entirely secondary to adjudged likelihood of HIT based on Pre-Test Scoring System’s Score. Essentially, the prospective design for eliciting incidence of HIT would have been better wherein specific subsets of patient populations (say cardiac surgery patients or vascular surgery patients) within the institution could have been followed for specific exposure of UFH/LMWH and corresponding incidence of PF4A/SRA positivity and thereafter the incidence of HIT with or without thrombosis. Alternatively, the retrospective design could have explored laboratory data concurrently or solely (with or without exploration of pharmacy database for argatroban and other related therapeutic agents for HIT) to explore the incidence of PF4A screening (true suspected HIT incidence across the system) and thereafter SRA confirmation (true confirmed HIT incidence across the system) during the study period across our university hospital. Interestingly, such retrospective design would have been able to identify the number of unique patients who were tested for PF4A or SRA and if multiple recurrence of HIT was suspected or confirmed in the same patients over the years.

Conclusion

Based on our retrospective review at university hospital during 2009-2013, the presumed incidence of HIT based on PF4A confirmation was at least 2 admissions among every 10,000 admissions receiving UFH and/or LMWH while the true incidence of HIT based on SRA positivity was at least 3 admissions among every 100,000 admissions receiving UFH and/or LMWH. Each admission during the five-year period where UFH and/or LMWH was used had an additional hospital cost of at least 2.22 “argatroban” US Dollars with patient/third-party-payer charge of at least 18.42 “argatroban” US Dollars as a reflection of our institutional economic burden secondary to suspected/confirmed HIT among our patient admissions.

Acknowledgements

The authors are indebted to Yaseer Al-Baghdadi, MD, Former Staff Anesthesiologist for seeding the thought for this project and Xavier Bell, Field Engineer, Department of Pharmacy, Harper Hospital, Detroit Medical Center, Detroit, Michigan, United States for extracting data from pharmacy database so as to enlist the patients for our retrospective review.

References

13. GREINACHER A, FARBER B, KROLL H, KOHLMANN T, WARKENTIN TE, EICHLER P: Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408


### Tables

#### Table 1: Incidence Of Heparin-Induced Thrombocytopenia Based On Heparin Exposure

<table>
<thead>
<tr>
<th></th>
<th>YEAR 2009</th>
<th>YEAR 2010</th>
<th>YEAR 2011</th>
<th>YEAR 2012</th>
<th>YEAR 2013</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions where only UFH was used</td>
<td>8981</td>
<td>9139</td>
<td>11103</td>
<td>13275</td>
<td>13281</td>
<td>55779</td>
</tr>
<tr>
<td>Admissions where only LMWH was used</td>
<td>1277</td>
<td>1405</td>
<td>1133</td>
<td>975</td>
<td>629</td>
<td>5018</td>
</tr>
<tr>
<td>Admissions where both UFH+LMWH were used</td>
<td>596</td>
<td>590</td>
<td>541</td>
<td>604</td>
<td>853</td>
<td>3453</td>
</tr>
<tr>
<td>Admissions where UFH and/or LMWH were used</td>
<td>10855</td>
<td>11104</td>
<td>12777</td>
<td>14754</td>
<td>14762</td>
<td>54025</td>
</tr>
</tbody>
</table>

Pharmacy Data and Laboratory Data Where HIT Was Suspected/Confirmed

<table>
<thead>
<tr>
<th></th>
<th>At Least 1</th>
<th>At Least 4</th>
<th>At Least 18</th>
<th>At Least 23</th>
<th>At Least 14</th>
</tr>
</thead>
</table>
| UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; PF4A: Platelet factor 4 antibody; HIT: Heparin-induced thrombocytopenia

#### Table 2: Comparative Data Based On Platelet Factor 4 Antibody Positivity

<table>
<thead>
<tr>
<th></th>
<th>Platelet Factor 4 Antibody Negative ruling out Heparin-Induced Thrombocytopenia (n=46)</th>
<th>Platelet Factor 4 Antibody Positive confirming Heparin-Induced Thrombocytopenia (n=18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64±13.4</td>
<td>66±14</td>
<td>0.82</td>
</tr>
<tr>
<td>Sex (% females)</td>
<td>41%</td>
<td>61%</td>
<td>0.17</td>
</tr>
<tr>
<td>Ethnicity (% African Americans)</td>
<td>53%</td>
<td>61%</td>
<td>0.009</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28.8±10.3</td>
<td>29.7±6.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Platelet counts at admission (K/uM)</td>
<td>184±17.5</td>
<td>205.5±10.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Platelet counts at discharge/emerg (K/uM)</td>
<td>128.5±68.1</td>
<td>214.5±100.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Platelet counts made during admission (K/uM)</td>
<td>38±133.2</td>
<td>56±134.9</td>
<td>0.75</td>
</tr>
<tr>
<td>Percent decrease in platelet counts from admission to nadir</td>
<td>63%±22%</td>
<td>64%±27%</td>
<td>0.83</td>
</tr>
</tbody>
</table>

UFH: Unfractionated heparin; LMWH: Low molecular weight heparin; PF4A: Platelet factor 4 antibody; HIT: Heparin-induced thrombocytopenia