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Concurrent Heparin-Induced and Valproate-Induced Thrombocytopenia Following Transcatheter Aortic Valve Replacement: A Diagnostic Challenge

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Abstract

Heparin and valproate are recognized causes of drug-induced thrombocytopenia. A 67-year-old man developed thrombocytopenia after transcatheter aortic valve replacement, with intraprocedural unfractionated heparin serving as the likely sensitizing exposure. Divalproex sodium was started for presumed postoperative delirium. Positive ELISA and serotonin release assay confirmed heparin-induced thrombocytopenia (HIT); apixaban was initiated at a reduced dose and later increased at outpatient follow-up. Platelet counts recovered gradually over the following weeks, both during and after valproate treatment, and normalized approximately four weeks after valproate discontinuation. A possible contribution of valproate to the prolonged thrombocytopenia was considered. However, delayed resolution of HIT and the concurrent therapeutic interventions remained competing explanations, and a definitive diagnosis of an independent valproate-induced process could not be established. This case demonstrates that incomplete or delayed platelet recovery despite HIT treatment should prompt systematic evaluation for additional drug-induced etiologies while maintaining appropriate diagnostic uncertainty.

Categories: Hematology, Internal Medicine, Cardiac/Thoracic/Vascular Surgery
Keywords: apixaban, delirium, drug-induced thrombocytopenia (dit), heparin-induced thrombocytopenia (hit), refractory thrombocytopenia, serotonin release assay, tavr, thrombocytopenia, valproic acid

Introduction

Drug-induced thrombocytopenia (DIT) occurs in approximately 25% of acutely ill patients and represents a frequent diagnostic challenge in hospitalized populations [1]. More than 1,400 medications have been implicated in thrombocytopenia, with heparin and valproate both well-recognized as causes of thrombocytopenia [1,2]. To identify any prior concurrent occurrence in the literature, we performed a focused literature search using PubMed with the terms "heparin-induced thrombocytopenia," “valproate,” and “thrombocytopenia." No prior report of concurrent heparin-induced thrombocytopenia (HIT) and valproate-induced thrombocytopenia was identified.

HIT is an immune-mediated, prothrombotic disorder characterized by antibodies directed against platelet factor 4 (PF4)-heparin complexes [3,4]. In contrast, valproate-induced thrombocytopenia (VIT) is generally a dose-dependent, nonimmune process associated with bone marrow suppression and impaired platelet production [5]. These entities differ substantially in pathophysiology, diagnosis, management, and clinical consequences. We describe a case of confirmed HIT following transcatheter aortic valve replacement (TAVR) in which a possible superimposed contribution of valproate to prolonged thrombocytopenia was considered, highlighting the diagnostic and therapeutic challenges posed by potentially coexisting prothrombotic and hemorrhagic forms of DIT.

Case Presentation

A 67-year-old man with severe aortic stenosis underwent recent TAVR (Day 0) and subsequently presented with acute altered mental status (Day 7). Prior to presentation, he had been living independently without a history of dementia or cognitive impairment. Family members reported abrupt behavioral changes, including repetitive questioning and episodes of confusion regarding familiar objects and circumstances. There was no history of trauma, loss of consciousness, or substance use.

Initial laboratory evaluation (Table *1*) revealed thrombocytopenia with a platelet count of 51,000/µL, compared to a baseline platelet count of 165,000/µL documented during his recent TAVR hospitalization approximately one week earlier. During that admission, he had received intraprocedural unfractionated heparin during the TAVR procedure itself. No heparin products were initiated during the index admission. The 4Ts score calculated on admission was 5 points, indicating an intermediate probability of HIT. Computed tomography of the head demonstrated no acute intracranial abnormality, and magnetic

resonance imaging revealed only stable age-related changes without evidence of acute infarction. Because his agitation and behavioral symptoms were attributed to postoperative delirium, divalproex sodium 125 mg daily was initiated on Day 9, following geriatric consultation, as prolonged QTc hindered the initiation of olanzapine. The platelet count reached its nadir of 15,000/µL also on Day 9. No serum valproate concentration was measured during the admission. Verification of the automated platelet count was done by smear review and showed no specimen clots. The patient's overall clinical timeline and the platelet trend throughout hospitalization are illustrated in Figure *1*.

Test	Patient value	Reference value
HIT ELISA	1.994 OD	0.000–0.400 OD
SRA, low-dose heparin	100% serotonin release	0–20%
SRA, high-dose heparin	2% serotonin release	0–20%
SRA interpretation	Positive	Not separately provided
Prothrombin time	13.2 seconds	9.4–13.5 seconds
INR	1.19	0.9–1.1
D-dimer	>7.650 µg/mL FEU	≤0.500 µg/mL FEU
Fibrinogen	76; units not verified	Not provided
Haptoglobin	<8.1 mg/dL	30–200 mg/dL
Reticulocyte percentage	2.56%	0.70–2.80%
Absolute reticulocyte count	0.120 ×10⁶/µL	0.026–0.168 ×10⁶/µL
Immature reticulocyte fraction	19.2%	2.3–15.9%
Reticulocyte hemoglobin	31.7 pg	28.2–36.5 pg
Direct antiglobulin test	Negative	Not provided
ADAMTS13 activity	>100.0%	>66.8%
Erythrocyte sedimentation rate	46 mm/hr	0–20 mm/hr
C-reactive protein	0.58 mg/dL	≤0.50 mg/dL
Hepatitis B surface antigen	Nonreactive	Nonreactive
Hepatitis A IgM antibody	Nonreactive	Nonreactive
Hepatitis B core IgM antibody	Nonreactive	Nonreactive
Hepatitis C antibody	Reactive	Nonreactive
HCV RNA, quantitative	Not detected	Not provided
HIV-1/HIV-2 antibody	Nonreactive	Nonreactive
Peripheral blood flow cytometry	No evidence of abnormal myeloid maturation or an increased blast population; no evidence of a lymphoproliferative disorder.	
Bilateral lower-extremity venous duplex ultrasonography	No deep vein thrombosis in either lower extremity.	

TABLE 1: Thrombocytopenia workup

HIT: heparin-induced thrombocytopenia; ELISA: enzyme-linked immunosorbent assay; OD: optical density; SRA: serotonin release assay; INR: international normalized ratio; FEU: fibrinogen-equivalent units; IgM: immunoglobulin M; HCV: hepatitis C virus; HIV: human immunodeficiency virus; ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

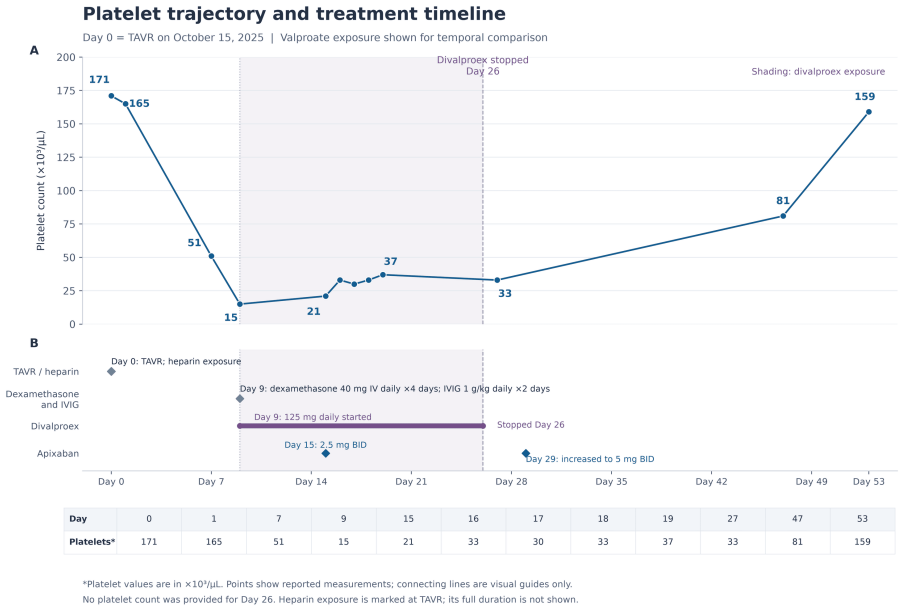


FIGURE 1: Platelet trajectory and treatment timeline following TAVR

Day 0 is the date of TAVR, October 15, 2025. (A) Reported platelet counts from Day 0 through Day 53 (December 7, 2025). (B) Timing of TAVR and heparin exposure, initiation of dexamethasone and intravenous immunoglobulin on Day 9, divalproex exposure, and apixaban initiation on Day 15 and dose escalation on Day 29. Shading indicates divalproex treatment from Day 9 through discontinuation on Day 26. Platelet counts are expressed as ×10³/μL. Points represent reported measurements, and connecting lines are visual guides rather than additional measured or interpolated values. No platelet measurement was provided for Day 26. The full duration of heparin exposure is not depicted.

TAVR: transcatheter aortic valve replacement; HIT: heparin-induced thrombocytopenia; IVIG: intravenous immunoglobulin; IV: intravenous; BID: twice daily.

Hematology was consulted for progressive thrombocytopenia. Given the profound thrombocytopenia and the absence of documented thrombosis with negative duplex ultrasound of bilateral lower extremities, immune thrombocytopenia was initially considered. The patient received dexamethasone 40 mg intravenously daily for four days and intravenous immunoglobulin (IVIG) 1 g/kg daily for two days, both initiated on Day 9. The platelet response was minimal.

Subsequent testing demonstrated a positive HIT enzyme-linked immunosorbent assay (ELISA; optical density 1.994) and a confirmatory serotonin release assay (SRA; 100% serotonin release), establishing the diagnosis of HIT. Additional laboratory evaluation was performed to evaluate for alternative etiologies; selected results are summarized in Table *1*.

The hematology team initiated apixaban at a dose of 2.5 mg twice daily (platelet count 21,000/μL), to mitigate risk of bleeding from low platelet count, recent TAVR, and history of lower GI bleeding. The dose was eventually increased to 5 mg twice daily at follow-up on discharge. Following initiation of non-heparin anticoagulation, platelet counts began to recover slowly but remained in the 33,000-37,000/μL range. Because platelet recovery remained incomplete, additional causes of thrombocytopenia were reconsidered, and divalproex sodium was discontinued.

Discussion

This case illustrates the diagnostic and therapeutic complexity that can arise when multiple drug-induced thrombocytopenic mechanisms occur simultaneously. HIT is mediated by IgG antibodies directed against PF4-heparin complexes, resulting in platelet activation, thrombin generation, and a paradoxical prothrombotic state despite thrombocytopenia [3]. Approximately one-half of patients with confirmed HIT develop thromboembolic complications, with the incidence of thrombosis ranging from 50 to 89% in untreated patients [3,4].

In contrast, VIT is generally a dose-dependent, nonimmune process associated with direct bone marrow suppression and impaired megakaryopoiesis [5]. Beyond thrombocytopenia, valproate causes inhibition of the secondary phase of platelet aggregation [5], with significant decreases in collagen-, arachidonic acid-, and ADP-mediated aggregation that correlate with both dose and plasma concentration, as well as

prolonged bleeding time, hypofibrinogenemia, coagulation factor deficiencies, and acquired von Willebrand disease [6]. The coexistence of HIT and VIT therefore creates a unique clinical paradox: HIT necessitates prompt anticoagulation to prevent thrombosis [7], whereas severe VIT may increase bleeding risk through both thrombocytopenia and platelet dysfunction [6].

Diagnosis was further complicated by the expected thrombocytopenia frequently observed after TAVR. This occurs in 69% to 87% of patients, with an average platelet count decline of approximately 40% (range 34%-45%), a nadir at 48 hours, and typical recovery by day 7 [8,9]. Severe thrombocytopenia (platelet count ⩽50 × 10^9/L) occurs in 2% to 6% of TAVR patients and is independently associated with one-year mortality (HR 3.44, 95% CI 1.02-11.6) [8,9]. The platelet trajectory in our patient differed from this expected pattern in magnitude and timing: the count fell by approximately 69% (165,000 to 51,000/μL) by the time of the index admission and reached a nadir of 15,000/μL two days later, with recovery extending over several weeks. A later and more prolonged nadir than the typical 48-hour postprocedural pattern may suggest a superimposed drug-induced or immune-mediated process, although the available data do not by themselves establish a specific second etiology. Post-procedural platelet declines occur in most patients and may obscure recognition of superimposed drug-induced etiologies. In addition, clinical prediction tools such as the 4Ts score may be less reliable when multiple alternative explanations for thrombocytopenia coexist [3,4]. As a result, clinicians may underestimate the likelihood of HIT when other plausible causes are present.

The development of postoperative delirium introduced an additional layer of complexity. Post-TAVR delirium occurs in approximately 10% to 22% of patients when assessed with validated tools and is independently associated with increased mortality [10-12]. In this case, delirium prompted initiation of valproate, thereby introducing a second thrombocytopenic medication during evaluation of an already evolving thrombocytopenic process. This sequence represents an iatrogenic cascade in which TAVR necessitated heparin exposure, postoperative delirium prompted valproate initiation, and the resulting overlap of thrombocytopenic mechanisms complicated both diagnosis and management.

Management required balancing competing thrombotic and hemorrhagic risks. Once HIT was confirmed, all heparin products were discontinued, and non-heparin anticoagulation was initiated. However, the persistent thrombocytopenia despite appropriate HIT therapy prompted reassessment of the medication profile and recognition of a possible second contributing process.

The strongly positive PF4/heparin ELISA (OD 1.994) and SRA (100% serotonin release) support a robust HIT antibody response. Because thrombocytopenia was already severe at the time of valproate initiation and platelet counts only minimally increased during valproate treatment before increasing further after its discontinuation, spontaneous resolution of HIT may have coincided with valproate withdrawal. The temporal relationship between drug discontinuation and platelet recovery must be interpreted cautiously given the concurrent interventions. Additional limitations include the absence of a serum valproate concentration, which precludes assessment of dose-dependency, and the absence of a formal causality assessment using a validated instrument. A retrospective Naranjo assessment was limited by thrombocytopenia preceding valproate exposure and confirmed HIT as an alternative explanation. No serum valproate concentration was measured, and rechallenge was neither feasible nor ethically appropriate.

It is important to note that prophylactic anticoagulation is insufficient to prevent thromboembolic complications [1]. Alternative anticoagulants recommended for the treatment of HIT include direct thrombin inhibitors as well as factor Xa inhibitors [3]. In our patient, a factor Xa inhibitor (apixaban) was selected. Given patient factors, it was initially started at a lower dose and was eventually increased to the treatment dose when the patient did not develop any bleeding. For isolated HIT, anticoagulation is generally continued for 4-6 weeks and may be extended up to three months depending on thrombotic risk [1]. Concurrently, suspected VIT necessitated reassessment of the need for ongoing therapy; although dose reduction may be considered in mild cases, discontinuation is often preferred in the setting of significant thrombocytopenia, particularly when another platelet-lowering condition is present [5]. Because VIT is typically reversible, with platelet recovery often occurring within approximately two weeks after drug withdrawal, serial platelet monitoring is essential to document hematologic recovery and guide ongoing management [6]. Current evidence supports prioritizing non-pharmacological multicomponent interventions for post-TAVR delirium, avoiding benzodiazepines and anticholinergic agents when possible, and reserving antipsychotics for carefully selected cases [13,14]. Delirium is also independently associated with increased one-year mortality after TAVR (hazard ratio, 3.02; 95% confidence interval, 1.75-5.23; P < .001) [15]. The coexistence of both delirium and thrombocytopenic complications after TAVR, which are individually associated with increased mortality, can possibly confer additional morbidity and mortality risk.

This case underscores the importance of multidisciplinary collaboration among cardiology, hematology, neurology, geriatrics, and clinical pharmacy teams [2]. Careful medication reconciliation and ongoing reassessment of the differential diagnosis were essential in identifying the contribution of each thrombocytopenic mechanism [2].

Conclusions

This case describes a patient with confirmed HIT following TAVR in whom a possible superimposed contribution of valproate to prolonged thrombocytopenia was considered but could not be definitively established. We highlight the diagnostic challenges posed by potentially overlapping drug-induced etiologies and demonstrate how expected postprocedural thrombocytopenia and postoperative delirium can further obscure recognition of superimposed causes. Delayed platelet recovery despite HIT-directed therapy should prompt systematic evaluation for additional thrombocytopenic processes, including a careful medication review; however, a temporal association alone is insufficient to establish causality, and delayed resolution of HIT should remain in the differential diagnosis. Early recognition and coordinated multidisciplinary management are critical to balancing thrombotic and hemorrhagic risks and optimizing patient outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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