

Exogenous C1-Esterase Inhibitor Prophylaxis during Complex Aortic Valve Replacement in a Patient with Hereditary Angioedema

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Abstract

Hereditary angioedema (HAE) is an inherited deficiency of C1-inhibitor (C1INH). HAE attacks can be triggered by many factors, including surgery. We present a case of a 60-year-old male, with endocarditis and a history of HAE, who required complicated aortic valve replacement. C4 level, C1-esterase inhibitor level, and C1 INH function were measured peri-operatively and on POD2. Peri-operative prophylaxis of HAE was accomplished using plasma-derived human C-esterase concentrate, administered pre-operatively and prior to extubation, to maintain C1INH level. No complications were encountered using this approach. The patient was discharged on POD15 and remains well at follow-up two years post-operatively.

Keywords: C1-Esterase Inhibitor; Prophylaxis; Hereditary Angioedema

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant inherited deficiency of C1-inhibitor (C1INH) which results in activation of the kinin and fibrinolytic systems, with bradykinin production, that contributes to angioedema [1]. In the USA, the prevalence is in 1: 50,000. A number of triggers are known to precipitate angioedema including surgery. Angioedema attack during surgery can be fatal with mortality rates between 15 - 33% [2]. The perioperative management of patients with HAE undergoing cardiac surgery is not uniform. The minimum C1INH and functional active serum C1INH levels that can permit safe surgery is not well established.

Case Report

We present a case of a 60-year-old African American male with endocarditis and a history of HAE that had been managed by methyltestosterone (Android®) 10 mg PO daily for 3 years. He presented with a 4 week history of worsening shortness of breath. On examination he had systolic and diastolic murmurs, leg edema, respiratory crackles and pulmonary edema on chest X-ray. The WBC was 8.11×10^3 . Echocardiography, revealed the presence of severe aortic regurgitation and vegetations on the aortic valve. Blood cultures were positive for *Gemella morbillorum*. He was started on antibiotics (Gentamicin 100 mg IV Q8H; and Ceftriaxone 2 gm IV Daily) and prepared for aortic valve replacement.

Preadmission prophylactic methyltestosterone was converted to danazol 200 mg PO TID on the evening prior to the operation. In addition plasma-derived C-esterase inhibitor, human concentrate (Berinert®) 20 U/kg (1500 IU) was administered prior to initiation of

cardiopulmonary bypass (CPB). Standard cardiac anesthesia preparation/monitoring was used. Anesthesia was maintained with 4.5% desflurane.

The C4 level, C1-esterase inhibitor level, and C1 INH function were measured after induction, and were measured at 22 mg dL⁻¹ (normal: 10 - 50 mg dL⁻¹), 11 mg dL⁻¹ (normal: 21 - 39 mg dL⁻¹) and C1 53% (normal: > 67%), respectively.

After initiation of CPB, systemic and topical hypothermia, and retrograde blood cardioplegia, were used for myocardial protection. The aortic valve was bicuspid with vegetations. A root abscess extended into the anterior leaflet of the mitral valve. After extensive debridement, the left ventricular outflow tract was reconstructed with bovine pericardium and the valve replaced with a 23 Epic bioprosthetic valve (St Jude). The aortic cross-clamp time was 185 minutes. Weaning from CPB was uneventful. A delayed sternal closure, using an Esmarch covering approach, was used due to concerns for possible postoperative hemodynamic issues. The chest was closed the next day, and the patient was extubated uneventfully on POD-2.

Danazol administration had been restarted on POD1 to control the HAE state. Measurement of the C4 level, C1-esterase inhibitor level, and C1-INH function were repeated on POD1, and the levels were 13 mg dL⁻¹, 17 mg dL⁻¹ and 76%, respectively.

Plasma-derived C1-esterase inhibitor concentrate 1500 IU was administered again, on POD2, before the patient was extubated. C4 level, C1-esterase inhibitor level, and C1 INH function measured on POD2, were 18 mg dL⁻¹, 21 mg dL⁻¹ and 88%, respectively. Finally, C4 level was measured to be 32 mg dL⁻¹ on POD13. Measured perioperative complement concentrations are illustrated in figures 1-3.

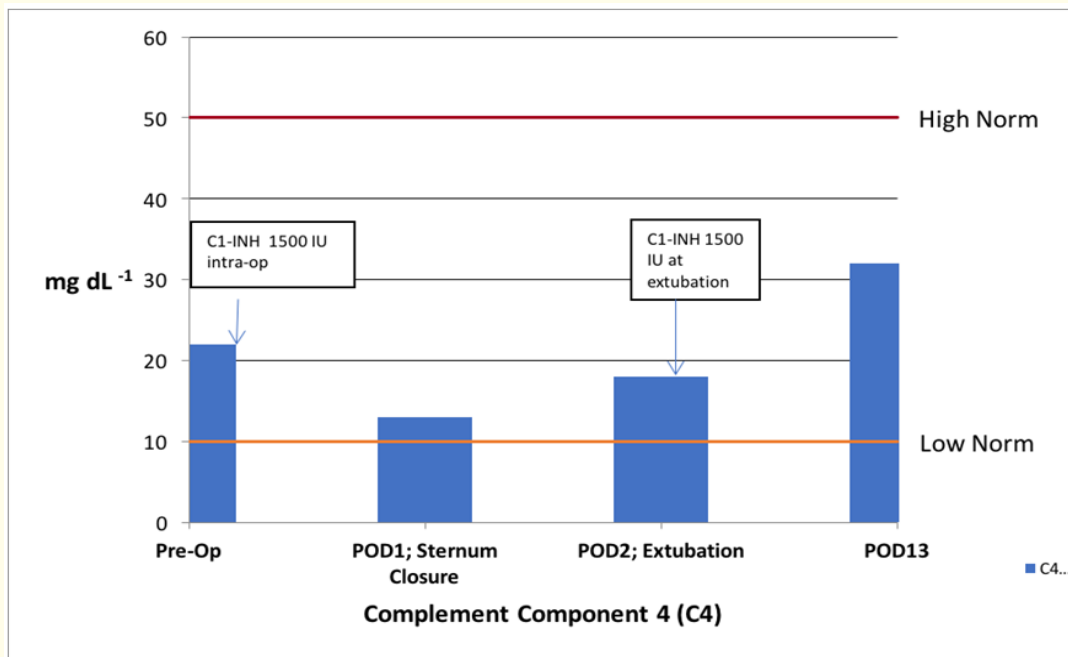


Figure 1: C4 level before and after the plasma-derived C1-INH concentrate replacement.

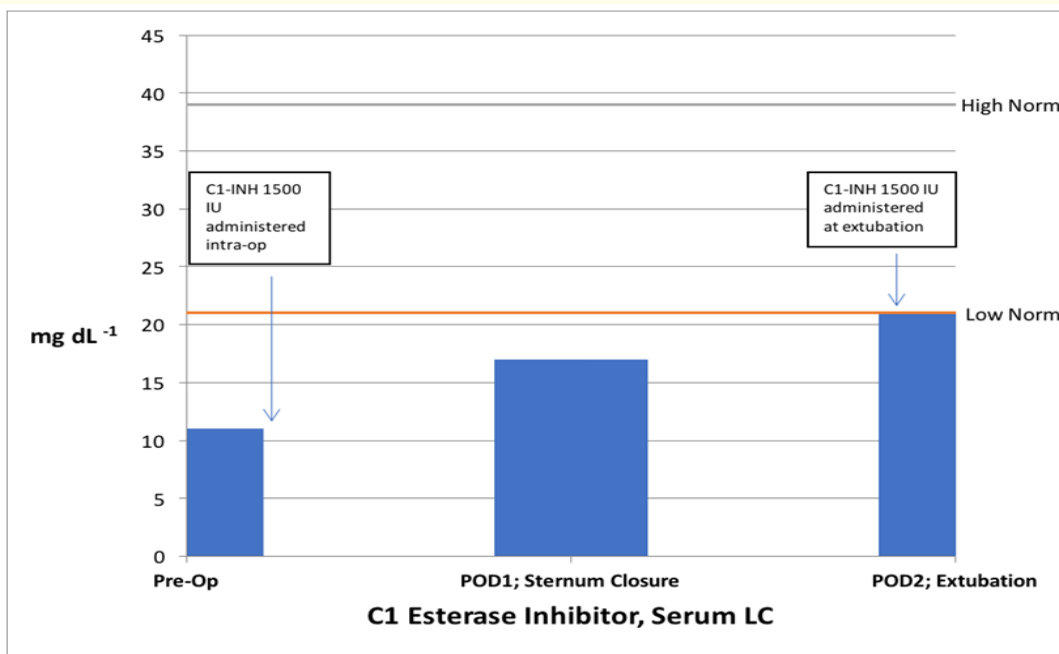


Figure 2: C1 esterase inhibitor level before and after the plasma-derived C1-INH concentrate replacement.

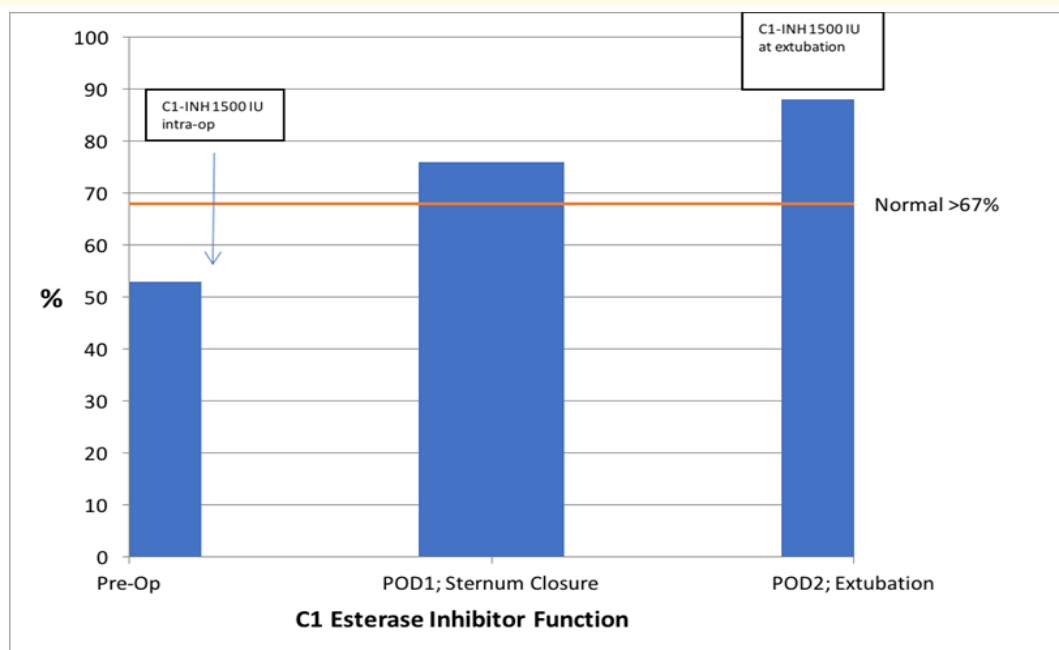


Figure 3: C1 esterase inhibitor function before and after the plasma-derived C1-INH concentrate replacement.

The patient exhibited no postoperative symptoms associated with HAE, such as anasarca or laryngeal edema. The duration of ICU stay was 4 days postoperatively, and he was successfully discharged on POD15. Danazol therapy was continued through POD10. On POD11, danazol was discontinued, and methyltestosterone 10 mg PO Daily was restarted and continued upon discharge. There were no complications encountered using this approach. The patient remains well at follow-up two years post-operatively.

Discussion

The perioperative management of patients with HAE who require cardiac surgery continues to evolve [3]. Several factors may trigger the onset of life-threatening HAE attacks. Extracorporeal circulation may be another triggering factor, by promoting complement activation [3].

In terms of anesthesia and surgery, the goal of short-term prophylaxis with plasma-derived C1-INH concentrate is to prevent an HAE attack [4,5]. This agent increases C1-INH levels by more than 50% within 30 minutes and the level remains above the baseline for 3 - 4 days.

The pharmacotherapy of HAE consists of three approaches: acute treatment, short-term prophylaxis, and long-term prophylaxis. C1 esterase inhibitors, FFP, kinin pathway inhibitors, antifibrinolytic agents, androgen steroids, and spasmolytic preparations are pharmacological agents for these three approaches [4,5]. There are a number of reports that describe successful open-heart surgery in HAE patients using exogenous source of C1-INH, either from pooled plasma, or by use of monoclonal manufactured product, the latter being more expensive [3]. The reported half-life of commercially available pooled products ranges from 18.4 - 56 hours, and that of the monoclonal product is 2.5 hours. Codispute reported the first case of HAE successfully managed with prophylactically administered C1-INH in the USA for cardiac valve reconstruction with a cardiopulmonary bypass pump [6].

The manifestations and severity of HAE are highly variable and unpredictable. Therefore, the "safe" level of C1INH and functionally active serum C1-INH levels during cardiac surgery in HAE patients is still not clear. Tappeiner recommended that C1-INH should be at least 50% of normal levels in HAE patients undergoing surgery [7]. Exogenous C1-INH replacement has been described for stabilizing safe C1INH levels.

Aside from replacement of C1-INH, several factors effect complement activation or deficiency. While hemodilution during cardiopulmonary bypass can reduce C1-INH concentrations to 30 - 50%, systemic inflammatory response increases complement levels. Another factor related to CPB is hemofiltration, which has been reported to reduce bradykinins (molecular weight 1100 Da) and cytokines. However, while ultrafiltration significantly filters TNF- α , it does not remove other mediators of inflammatory response, including C4 and c1h. Mild hypothermia inhibits systemic and cerebral complement activation. It has been shown that C4, C3, and C5 activation significantly increase at clinical hypothermia temperatures.

C1-INH replacement is usually given before anesthesia and prior to initiation of CPB. In some cases, with a history of psychological stress-induced attacks, therefore C1-INH is given the night before surgery, as well.

In our case, as the patient was on Danazol preoperatively for 1 day, and the level of C4 and C1-INH functional activity was 53%, therefore we did not give C1-INH concentrate before anesthesia induction. We measured the level of C4 level, C1-esterase inhibitor level, C1-INH function during anesthesia. Additional C1-INH was given before CPB because the measured complement levels were reduced after induction, and CPB is a trigger factor. We also gave second dose prior to extubation to prevent laryngeal HAE attack. We also decreased the CPB prime volume, to decrease hemodilution, and added mannitol and albumin for free radical scavenging and contact activation reduction effects.

In the future, direct inhibition of the kallikrein-kinin system may be a strategy to prevent the induction of HAE. Lanadelumab (DX-2930), a human monoclonal antibody that targets the kallikrein-kinin system, has shown promise in the prophylactic management of HAE patients with C1-esterase deficiency. It was shown to reduce the frequency of HAE episodes by 88-100% over the 50-day study period [8].

Conclusion

In summary, although there are no universally accepted guidelines regarding management of patient's with HAE undergoing cardiac surgery, the availability of pooled or monoclonal C1-INH concentrate allows for its timely administration to prevent induction of an attack.

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