SUCCESSFUL USE OF C1 ESTERASE INHIBITOR PROTEIN IN A PATIENT WITH HEREDITARY ANGIONEUROTIC EDEMA REQUIRING CORONARY ARTERY BYPASS SURGERY

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Hereditary angioneurotic edema (HANE) is an inherited deficiency of an inhibitor protein (C1INH) that inactivates the activated first component (C1) of the classical complement pathway. With deficiency of C1INH, there is an unimpeded action of activated C1 producing a depletion of the complement proteins and concurrent accumulation of their breakdown products. The result can be a marked increase in vascular permeability and a coagulopathy.¹ HANE is characterized by episodic attacks with reported mortality rates of 15% to 33%; surgery is a recognized trigger.¹ This report is the first to document the use of C1INH concentrate (C1INH Inhibitor TIM3, Baxter Healthcare Corp, Edwards Division, Deerfield, Ill) with cardiopulmonary bypass (CPB).

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Clinical summary. A 53-year-old white man (height 169 cm, weight 70 kg) with triple vessel disease, a left ventricular ejection fraction of 30%, and unstable angina was referred for urgent coronary artery bypass grafting (CABG). A 20-year history of HANE with episodic life-threatening facial and limb edema had been successfully controlled for only the previous 7 years with danazol (Danocrine, Sanofi Winthrop), 200 mg daily. Preoperatively, total (C1INH-I) and functional (C1INH-F) serum C1INH concentrations were 0.11 mg/dL (normal range 0.19-0.43 mg/dL) and 0.28 U/mL (normal range 0.8-1.2 mg/dL), respectively (Figs 1A and 1B).

Sixty minutes before anesthetic induction, 1000 units of intravenous C1INH was given. CABG was performed with CPB, hypothermia to 32°C, and with antegrade and retrograde blood cardioplegia. The left internal thoracic artery was grafted to the left anterior descending coronary artery, and 2 saphenous vein grafts were anastomosed to the circumflex and right coronary arteries (aortic crossclamp time 31 minutes, CPB time 51 minutes).

The patient was extubated 8 hours after an uneventful operation. One hour before extubation, 1000 units of intravenous C1INH was given to minimize the potential for laryngeal edema from endotracheal intubation. No evidence of a bleed-

Fig 1A. Total (C1INH-I) serum C1INH levels at the following measurement times: *Preop*, baseline; *or 1415*, before heparinization; *or 1500*, before CPB; *or 1510*, +10 minutes of CPB; *or 1520*, +20 minutes of CPB; *or 1530*, +30 minutes of CPB; *or 1540*, +40 minutes of CPB; *or 1600*, after CPB; *or 1620*, after total protamine dose; *day 1, 0900*, before extubation; *day 1, 1030*, +90 minutes after extubation; *day 1, 1630*, +7.5 hours after extubation; *day 1, 1930*, +12.5 hours after extubation.

ing diathesis or significant limb, face, or neck edema occurred, and he was discharged to his home 6 days later.

Discussion. HANE is an autosomal dominant disease with 2 variants: 85% of patients have a deficiency of C1INH and 15% of patients have normal serum levels but functionally inactive C1INH. The majority of patients do not require long-term drug treatment. Androgen therapy, which increases hepatic synthesis of C1INH, is recommended for frequent or life-threatening attacks.¹

Optimal perioperative management for HANE is unclear. Continuation of and/or several days of increased androgen before the operation, 2 units of fresh-frozen plasma 24 hours before the operation, and/or a short course of anti-fibrinolytic therapy have been recommended.^{1,4} Ostensibly, outcome will be determined by the interaction between the magnitude of the stressor (surgery) and the serum level of C1INH-I/F. Records of C1INH-I/F in reported cases are scarce. Hence such recommendations must be viewed with

caution.³ Importantly, no effective therapy exists for acute attacks.³

CPB is particularly challenging to these patients. First, the hemodilution associated with CPB is known to reduce serum C1INH levels by 30% to 50%.³ Second, complement activation occurs during CPB and with the administration of protamine. Furthermore, a safe lower level of C1INH is unknown.^{1,3} Therefore these patients may have uncontrolled complement activation.

Only 3 case histories of patients with HANE requiring CPB have been reported.^{2,3} One patient, a child with only biochemical evidence of HANE, had successful closure of an atrial septal defect.³ Haering and Comunale³ reported on a 71-year-old man receiving long-term stanozolol therapy who had an uncomplicated CABG. The dose of stanozolol was doubled for 5 days before the operation. This patient's baseline serum C1INH level was 0.11 mg/dL (75% of normal). No increase in C1INH was evident after 5 days of increased

Fig 1B. Functional C1INH-F serum C1INH levels. For legend, see Fig 1A.

androgen therapy. During CPB, serum C1INH concentration fell to a nadir of 0.6 mg/dL (38% of normal) after protamine administration.

Bonser and coworkers² reported on a 74-year-old patient requiring CABG who was on a program of long-term danazol therapy (200 mg daily) and received the drug until the day of the operation. Disseminated coagulopathy with generalized systemic and pulmonary edema immediately after CPB proved fatal. This patient's baseline C1INH level was 0.6 mg/dL (38% of normal). Bonser and colleagues² believed that a maintenance dose of androgen therapy was inadequate and suggested that higher doses should be administered for at least 1 week before the operation in the expectation that C1INH levels can be increased to greater than 50% of normal. They concluded that CPB in patients with C1INH deficiency is extremely hazardous. Neither Bonser's group² nor Haering and Comunale³ measured serum C1INH-F.

Our patient continued to receive androgen therapy until the time of the operation. We have demonstrated that 1000 plasma units of C1INH maintained the level of C1INH during CPB. There was no significant reduction in either total or

functionally active serum C1INH (Figs 1A and 1B) during 60 minutes of CPB. The further administration of 1000 units of C1INH before extubation doubled and maintained the serum C1INH-I/F for 48 hours. The half-life of C1INH is 18 hours (product information, Baxter Edwards Laboratories).

Therefore, depending on the baseline level, CPB can reduce the serum C1INH concentration, with fatal consequences. Hence measurement of preoperative serum C1INH-I/F is important. In conclusion, the prophylactic use of C1INH concentrate in patients with HANE requiring CPB prevents serum C1INH-I/F levels from decreasing. Uncontrolled complement activation is prevented and potentially fatal complications are thereby avoided. Given that a safe lower limit of C1INH is not known and conventional therapy for acute attacks is ineffective, the prophylactic use of C1INH concentrate is recommended.

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