Anaesthetic implications of hereditary angioneurotic oedema

Paul J. Poppers MD

Hereditary angioneurotic oedema (HANE) presents the danger of laryngeal oedema that may, among other causes, be triggered by the anaesthetist's manipulation of the patient's airway. Local and regional anaesthesia are usually recommended. This report pertains to a patient who successfully tolerated general endotracheal anaesthesia and whose management included prophylactic treatment with danazol and fresh-frozen plasma.

Hereditary angioneurotic oedema (HANE) is a disease involving the complement system. Disease expression is associated with abnormally low plasma levels of C_1 esterase inhibitor, or by the presence of functionless C_1 esterase inhibitor. A typical manifestation of the disease is the occurrence of oedema in various locations of the body, particularly the upper airway. Laryngeal oedema poses the greatest danger to the patient. HANE is therefore of grave concern to the anaesthetist.¹ Local and spinal anaesthesia has always been preferred in these patients,^{2,3} and general anaesthesia has been described, but with the recommendation that tracheal intubation be avoided.⁴ Successful general anaesthesia with tracheal intubation is not mentioned in the literature. It is therefore of interest to discuss the disease and to report a patient with HANE, in whom inhalation anaesthesia and tracheal intubation were indicated. Following prophylactic administration of danazol⁵ and fresh frozen plasma,⁶ the perioperative course proceeded uneventfully.

Case report

A thirty-year-old mentally retarded white female was admitted to the hospital for multiple dental restorations

and extractions. She had a 14-year history of HANE with multiple attacks of oedema that involved the extremities, but not the larynx. Her latest attack occurred approximately one year prior to admission. Two brothers had suffered from the same disease, the older one having died of laryngeal oedema.

The physical examination was essentially unremarkable except for extensive dental caries. The laboratory studies performed included chest radiograph, electrocardiogram, serum electrolytes, liver enzymes, blood urea nitrogen, urinalysis, complete haemogram and clotting parameters. All were within normal limits.

Complement studies demonstrated a normal C_1 esterase inhibitor level, a complement haemolytic assay of 87 CH50 units (control value 200 CH50 units), and a C_4 serum concentration of $8 \text{ mg} \cdot \text{dl}^{-1}$ (normal range 13–40 $\text{mg} \cdot \text{dl}^{-1}$). These values confirm the diagnosis of HANE. All patients with this disease have a decreased serum level of C_4 , whereas the haemolytic assay of complement usually yields low values, but may occasionally be normal. The normal C_1 esterase inhibitor level that is found in this patient indicates that the protein is functionally abnormal, a condition encountered in approximately 15 per cent of the HANE patient population, whereas 85 per cent have a normal C_1 esterase inhibitor but at abnormally low levels.

Danazol therapy was started ten days before admission with the daily administration of 300 mg by mouth. On the evening before surgery the patient received three units of fresh frozen plasma to supply functional C_1 esterase inhibitor. The next morning she took her usual dose of danazol. As premedication, 20 mg diazepam was administered orally.

Anaesthesia was induced with an intravenous injection of 350 mg thiopentone. Orotracheal intubation, facilitated by 100 mg succinylcholine IV, was accomplished atraumatically.

Anaesthesia was maintained with 60 per cent nitrous oxide in oxygen and 1.5–2 per cent enflurane. Its course was without incident. At the completion of surgery, no oedema of the face or extremities was noted. The trachea was extubated when the patient was responsive to vocal commands. Recovery was uneventful. The patient was discharged from the hospital the next day.

Key words

GENETIC FACTORS: hereditary angioneurotic oedema;
COMPLICATIONS: laryngeal oedema; ANAESTHETIC
TECHNIQUES: endotracheal; PHARMACOLOGY: danazol.

From the Department of Anesthesiology, State University of New York, Health Sciences Center, Stony Brook, New York 11794-8480.

Discussion

HANE was first described by Osler, one hundred years ago.⁷ It is inherited as an autosomal dominant disorder in which there is a deficient or abnormal inhibitor of the first component of the complement pathway.⁸ The fibrinolytic system may also be abnormal. There are no published data on the incidence of HANE, but reliable sources give estimates of 1:10,000. The acute development of circumscribed areas of oedema is common, often provoked by pressure or trauma. Though swelling can occur anywhere, areas of predilection are the skin of the face and extremities, the gastro-intestinal mucosa, and the upper airway. Oedema of the oropharynx, the larynx and the trachea is particularly dangerous. Its major causation is localized trauma, however minor. Anaesthetists therefore counsel against the use of general anaesthesia so as to avoid the pressure or trauma of oral, nasal or tracheal airways with resulting life-threatening respiratory obstruction.¹⁻⁴ Regional anaesthesia has been used without problems, and even general anaesthesia by mask, but without insertion of an artificial airway, has been tolerated.⁴

In view of the mental condition of the patient, local anaesthesia for oral surgery was not an option in this instance, and general endotracheal anaesthesia was the indicated alternative. However, nasotracheal intubation was considered to be potentially more dangerous than orotracheal intubation, and the latter was accomplished smoothly and atraumatically.

The precise pathogenesis of HANE is unknown.^{1,5} The complement system consists of at least nine plasma proteins, designated as C₁ to C₉. Upon activation, the system enhances many immune responses. The classical pathway for complement activation usually centres around antigen-antibody reactions, but the activation can also be triggered by immunoglobulin aggregates in an alternative pathway. Once activation has occurred, the complements become involved in a sequential manner, and in this cascade of reactions precursor proteins are converted into active enzymes. Thus, the first component, C₁, is converted to C₁ esterase. This activates the complement components C₂ and C₄, and C₃ turnover is increased.⁶ In the absence of C₁ esterase inhibitor, initial activation of C₁ is followed by uncontrolled and excessive activation of the complement cascade, with depletion of C₂ and C₄ and ultimate release of vaso-active peptides and lysis of cell membranes. As a result, vascular permeability is increased and oedema is formed. About 80-85 per cent of patients with HANE have a low level of C₁ esterase inhibitor. The remaining 15 per cent of patients have normal or elevated levels of a protein similar to C₁ esterase inhibitor, which, however, is functionally inactive.⁶

Attacks may occur spontaneously, but are often in-

duced by precipitating factors such as stress, menstruation, pregnancy, exposure to temperature extremes, physical exertion and, especially, trauma such as surgery. Dental extractions, whether performed with or even without the benefit of local anaesthesia, are particularly dangerous because of the resultant occurrence of life-threatening attacks of upper airway oedema and stridor, and which are associated with a 15-30 per cent mortality rate.^{1,3}

The disease often presents at puberty in an accelerated state. In other cases symptoms are already manifest before six years of age. However, in those pre-pubertal years, the respiratory and gastro-intestinal tracts are generally spared, and the lesions remain limited to the skin and subcutaneous tissue.¹

Therapeutic modalities include inhibitors of plasminogen activation, such as epsilon amino caproic acid and tranexamic acid.¹ These agents reduce attacks, but do not prevent them.⁵ Unlike angioedema resulting from allergic reactions, HANE does not respond to therapy with antihistamines, epinephrine or steroids.^{5,6} Drugs used more recently and offering effective prophylaxis^{5,6} are the androgens and modified androgens, the latter having more anabolic activity and fewer virilizing effects. One of these, danazol, is a pituitary gonadotropin inhibitor with mild, dose-related androgenic activity. Short-term prophylaxis has been achieved with administration of danazol for as little as ten days prior to dental or surgical procedures.⁹ The dose of danazol that prevents HANE attacks is variable, does not correlate with body mass or surface, and must be empirically determined in each patient. Initially, as much as 600 mg per day by mouth in three divided doses may be required. Subsequent dosage can be reduced in step-like fashion to a maintenance regimen of 200-300 mg daily.^{5,9,10}

The androgens act on the basic defect by increasing hepatic synthesis of C₁ esterase inhibitor, and the response is dose-related. In patients with dysfunctional C₁ esterase inhibitor, normal C₁ esterase inhibition is induced and both proteins can be detected. Side effects from these drugs include weight gain, alopecia, acne, hirsutism and menstrual irregularities.¹⁰ Occasionally, although rarely, allergic responses have occurred. With long-term therapy, headaches, neuromuscular dysfunction ranging from spasms to myalgias, microscopic haematuria, and mild transient liver dysfunction have been reported.¹⁰ The side effects disappear or decrease in severity after reduction of the drug dosage.

Fresh-frozen plasma contains C₁ esterase inhibitor. Therefore, a useful prophylactic alternative is to infuse two to four units of fresh-frozen plasma within 24 hours before surgery. Moreover, an acute attack can be terminated; clinical improvement can be obtained within forty

minutes following its infusion.¹¹ It results in an increase in serum C₁ esterase inhibitor of 2.5 mg·dl⁻¹ for every two units infused. The beneficial effect lasts one to four days, after which the C₁ esterase inhibitor returns to its previously low level. It is theoretically possible that fresh-frozen plasma not only provides C₁ esterase inhibitor, but also substrates like C₂ and C₄, which might tend to make the condition worse. In practice, this does not occur and fresh-frozen plasma is at present a major therapeutic modality.

It has been argued that a concentrate of C₁ esterase inhibitor purified from plasma is preferable to fresh-frozen plasma.¹² It eliminates the risk of hepatitis and the theoretical danger of concurrent C₂ and C₄ action. Additionally, it could be used in pregnant women, children and those other patients who cannot tolerate androgen therapy. However, the very high cost of purification limits practical application.

This case report lends credence to our opinion that patients with HANE can safely undergo general anaesthesia and oro-tracheal intubation when given a two-week prophylactic course with danazol and, additionally, fresh-frozen plasma on the evening before surgery. For emergency surgery, fresh-frozen plasma, because of its rapid effect, can be used prophylactically. Moreover, it has therapeutic value in case an acute attack should occur. However, upper airway obstruction may occur so acutely that, instead of fresh-frozen plasma, an immediate tracheostomy is the only acceptable therapy.

Acknowledgement

The author expresses his thanks and appreciation to Dr. Allen P. Kaplan, Professor and Head, Division of Allergy, Rheumatology and Clinical Immunology, Department of Medicine, State University of New York at Stony Brook, for his critique and suggestions.

References

- 1 Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and management. *Ann Int Med* 1976; 84: 580-93.
- 2 Gibbs PS, LoSasso AM, Moorthy SS, Hutton CE. The anesthetic and perioperative management of a patient with documented hereditary angioneurotic edema. *Anesth Analg* 1977; 56: 571-3.
- 3 Abada RP, Owens WD. Hereditary angioneurotic edema, an anesthetic dilemma. *Anesthesiology* 1977; 46: 428-30.
- 4 Schär B. Anaesthesie beim Patienten mit hereditärem Angioödem. *Anaesthesist* 1984; 33: 140-1.
- 5 Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol; reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976; 295: 1444-8.
- 6 Frank MM, Gelfand JA, Sherins RJ, Alling DW, Gadek J. The treatment of hereditary angioedema with danazol. In: Opferkuch W, Rother K, Schultz DR, eds. *Clinical Aspects of the Complement System*. Stuttgart: Georg Thieme, 1978, pp 134-7.
- 7 Gadek JE, Hosea SW, Gelfand JA, Frank MM. Response of variant hereditary angioedema phenotypes to danazol therapy. *J Clin Invest* 1979; 64: 280-6.
- 8 Osler W. Hereditary angioneurotic edema. *Am J Med Sci* 1888; 35: 37-9.
- 9 Pitts JS, Donaldson VH, Forristal J, Wyatt RJ. Remission induced in hereditary angioneurotic edema with an attenuated androgen (danazol): correlation between concentrations of C₁-inhibitor and the fourth and second components of complement. *J Lab Clin Med* 1978; 92: 501-7.
- 10 Hosea SW, Santaella ML, Brown EJ, Berger M, Katusha K, Frank MM. Long-term therapy of hereditary angioedema with danazol. *Ann Int Med* 1980; 93: 809-12.
- 11 Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. *J Allergy Clin Immunol* 1975; 55: 386-93.
- 12 Gadek JE, Hosea SW, Gelfand JA et al. Replacement therapy in hereditary angioedema; successful treatment of acute episodes of angioedema with partly purified C₁ inhibitor. *N Engl J Med* 1980; 302: 542-6.

Résumé

L'œdème angioneurotique héréditaire (HANE) présente le danger d'œdème laryngé qui peut, parmi d'autres causes, être déclenché par l'anesthésiste manipulant les voies aériennes. L'anesthésie locale et régionale sont souvent recommandées. Cette histoire de cas concerne un patient qui toléra avec succès l'anesthésie générale endotrachéale et dont la conduite comprenait un pré-traitement prophylactique avec le danazol ainsi que des plasmas pré congelés.