

Hereditary Angioedema Managed with Low-Dose Danazol and C1 Esterase Inhibitor Concentrate: A Case Report

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Abstract

Background: Hereditary angioedema (HAE) is a rare life-threatening disease that can occur in pregnancy.

Case: A nulliparous woman was diagnosed as having HAE at 22 weeks of gestation after a series of symptomatic episodes. Following an initial course of C1 esterase inhibitor (C1EI) therapy for an acute episode of HAE, she was treated with danazol for prophylaxis. Danazol did not prevent recurrence of symptoms, and its use was discontinued after six weeks. Thereafter, the patient was treated exclusively with C1EI at weekly intervals for exacerbations of her HAE. At 37 weeks' gestation, she delivered a healthy 3050 g female neonate. At the time of discharge the female neonate had no signs of virilization or congenital anomalies.

Conclusion: Low dose danazol was ineffective in treating this woman's HAE in pregnancy. The use of C1EI in pregnancy is associated with good outcomes.

Résumé

Historique : L'œdème angioneurotique héréditaire (OAH) est une maladie rare mettant en danger la vie de la patiente et qui peut se manifester pendant la grossesse.

Cas : On a diagnostiqué, chez une femme nullipare à 22 semaines de gestation, un cas de OAH à la suite d'une série d'épisodes symptomatiques. Suivant un traitement initial à l'inhibiteur de l'estérase C1 (C1EI) en raison d'un épisode aigu d'OAH, on lui a administré du danazol en prophylaxie. Le danazol n'a pas réussi à prévenir la récurrence des symptômes; on a donc interrompu l'administration au bout de six semaines. Par la suite, on a traité la

patiente exclusivement à l'aide du C1EI, à intervalles hebdomadaires, lorsqu'il y avait aggravation de son OAH. À 37 semaines, elle a donné naissance à une fille en santé de 3 050 g. Au moment où la patiente a obtenu son congé, le nouveau-né ne présentait aucun signe de virilisation ou d'anomalies congénitales.

Conclusion : L'administration à faible dose de danazol n'est pas parvenue à traiter l'OAH de cette patiente pendant la grossesse. L'utilisation du C1EI pendant la grossesse s'est traduite par de bonnes issues.

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INTRODUCTION

Hereditary angioedema (HAE), also known as C1 esterase inhibitor (C1EI) deficiency, is a rare inheritable disease caused by underproduction (type 1), dysfunction (type 2), or functional deficiency (type 3, abnormal protein binding) of C1 esterase inhibitor. This deficiency or dysfunction leads to episodes of angioedema of the skin, the gastrointestinal mucosa, and the mucosa of the upper airway. HAE occurs in approximately one in 50 000 people.¹ Since raised circulating levels of estrogen worsen the disease, pregnancy can induce an increase in the frequency and severity of attacks. These attacks of angioedema can be life-threatening if the airways become involved. In this report we describe a patient with HAE that was diagnosed in the 22nd week of pregnancy who was managed successfully with multiple doses of C1 esterase inhibitor (C1EI).

Key Words: Danazol, hereditary angioedema, hereditary angioneurotic edema, C1 esterase inhibitor deficiency, angioedema without urticaria, pregnancy

Competing Interests: None declared.

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THE CASE

A 22-year-old woman (gravida 2 abortus 1) was referred to the Maternal–Fetal Medicine (MFM) service at BC Women’s Hospital (BCWH) at 22 weeks of gestation, with a diagnosis of HAE. After the tenth week of pregnancy, she had made weekly trips to her local emergency department because of episodes of lower leg urticaria and edema. The local internal medicine consultant had made the diagnosis of HAE in her 21st week of gestation when testing showed her C1EI activity levels to be well below normal values. The patient was subsequently referred to the MFM service at BCWH for ongoing management.

In retrospect, the patient’s past history of symptoms was typical for individuals with HAE. The patient recalled having her first episode of peripheral angioedema at age 16; thereafter, she experienced episodes once or twice per year. The episodes typically began with swelling of the hands and feet that slowly extended proximally, culminating in abdominal pain, diarrhea, and dyspnea. Occasionally a jigsaw puzzle-like rash would appear on her chest. She would present to the local hospital emergency department on numerous occasions because of these symptoms, which were treated as allergic reactions. Treatments offered to her included antihistamines, bronchodilators, and adrenaline, all with little or no effect. On one occasion, she underwent a diagnostic laparoscopy because of the severity of abdominal pain. The abdominal pain was later attributed to the bowel edema that may occur in HAE.

The diagnosis of HAE was finally made at 22 weeks’ gestation by the local internal medicine consultant who found her C1EI activity level to be only 0.14 (C1EI activity is a functional assay expressed as a fraction of enzyme activity seen in a healthy population, with a normal range of between 0.7 and 1.3). Her past medical history was otherwise unremarkable. She had recently stopped smoking and denied use of alcohol or illicit drugs. Later, it was learned that her father also had HAE, as did a first cousin (whose parents were the siblings of the patient’s parents). On initial examination at BCWH, the patient had mild edema of the feet but no other abnormality. Ultrasound examination showed a normally grown female fetus with normal-appearing amniotic fluid. Following the initial MFM consultation, the patient had an episode of swelling of the hands together with diarrhea and abdominal pain, and she was admitted to the antepartum unit of BCWH for urgent treatment. She was given a dose of C1EI concentrate (1100 units) with excellent response. After discussing various therapeutic options to control her HAE, we elected to begin low-dose danazol (50 mg/day) prophylaxis with a supply of C1EI available for treatment of acute exacerbations. The patient was aware of the possibility of virilization of her

female fetus as a consequence of danazol therapy. Arrangements were then made for the patient’s antenatal care to be continued in her home community, with close liaison between her primary caregivers and tertiary care consultants.

After two weeks of danazol therapy, the patient continued to experience HAE attacks at intervals of approximately five days. The dose of danazol was increased to 100 mg/day. While on the higher dose, the patient began to experience symptoms attributed to the use of danazol (acne, excess weight gain, edema, and irritability). After four weeks of treatment at the higher dose, a decision was made to stop the danazol because there was no change in the frequency or intensity of the attacks, and the side effects were becoming problematic for the patient. Danazol therapy was discontinued after a total of six weeks of use. Subsequently the patient’s episodes of HAE were treated exclusively with C1EI in single doses of 1100 units. The frequency of the attacks necessitated C1EI infusions at weekly intervals, and because of the unstable nature of her disease we planned to have her undergo labour and delivery in the tertiary care facility (BCWH). We anticipated that the stress of labour and delivery would rapidly consume C1EI and that multiple doses of C1EI in labour would be required. Prophylactic C1EI was to be given in early labour, prior to any obstetric surgery, and again immediately after delivery.

The patient returned to BCWH at 36 weeks’ gestation in threatened labour. Over the following week she was given C1EI on two more occasions when it appeared that labour was beginning. At 37 weeks’ gestation, labour was induced by rupture of membranes after administration of prophylactic C1EI. After an unremarkable labour, the patient delivered a 3050 g female neonate with Apgar scores of 6, 7, and 9 at 1, 5, and 10 minutes, respectively. The neonate was subsequently shown to be healthy and had no signs of genitourinary anomalies or virilization. Two additional doses of C1EI were given, one during active labour and another immediately postpartum. Despite the three doses of C1EI given to the patient in the peripartum period, she suddenly developed swelling of the hands and constriction of the throat on the first postpartum day, requiring more C1EI therapy. In total, we used 22 doses of C1EI in the patient’s obstetric care.

The patient was discharged on the third postpartum day in good condition. Following her pregnancy, the frequency of episodes of HAE diminished, but the patient did not return to her pre-pregnancy frequency of attacks for one year. The mother reports that the child is developing normally in all respects (at 5 years of age).

DISCUSSION

Historically, HAE was known as angioneurotic edema, highlighting the influence that psychological stress had on the appearance of symptoms. A deficiency of C1EI leads to episodes of angioedema in different parts of the body, particularly the skin, the gastrointestinal mucosa, and the mucosa of the upper airway. The resulting clinical manifestations include non-pruritic, non-pitting edema of the periphery, recurrent severe episodes of nausea, vomiting, abdominal pain, and upper airway obstruction. In type 1 HAE, there is a deficiency of C1 esterase inhibitor, whereas in type 2, the C1EI is dysfunctional.¹ Type 3 HAE is a functional deficiency in which C1EI is abnormally bound to albumin.² This subset of HAE is aggravated by endogenous or exogenous estrogen and therefore worsens with estrogen ingestion, at menarche, and during pregnancy.^{3,4}

C1 esterase inhibitor is a glycosylated, 104 kDa serine protease inhibitor that is produced in the liver, in the placenta, and in macrophages. It is one of the main regulators of the classical complement pathway. C1EI acts on C1 esterase in the complement pathway, plasmin in the fibrinolytic pathway, Factor XI in the coagulation cascade, bradykinin, Hagemann factor, and kallikrein.^{1,2,5} In normal circumstances, immune complexes trigger the formation of C1 esterase which then acts on the substrates C4 and C2 to form the complex C2,4 (C3). This complex leads to the activation of vasoactive peptides and anaphylactoid-like substances. A deficiency of C1E inhibitor leads to inappropriate or premature activation of the complement pathway as C1 esterase activity goes unchecked.² Symptoms are the direct result of tissue edema, usually in the respiratory tract (larynx, bronchioles), gastrointestinal tract, or skin (face, limbs, genitalia). Tissue edema leads to symptoms such as swelling of the face, hands, and tongue, dyspnea, stridor, hoarseness, pain, nausea, vomiting, colic, and upper respiratory tract obstruction. Most patients do not develop urticaria, and symptoms may not develop until well into adolescence. Many patients attribute attacks to periods of stress (arising from causes such as trauma, viral illness, or dental work); the onset and duration of symptoms are variable, but symptoms usually last from 24 to 48 hours.^{1,2} Care must be taken in pregnant patients to differentiate between HAE and gastrointestinal or obstetric causes of abdominal pain.

HAE is commonly misdiagnosed as an allergic reaction, since angioedema is most often associated with allergies. The usual treatments for allergic reactions (such as epinephrine and antihistamine agents) are ineffective in HAE. The diagnosis should be suspected if there is a history of recurrent attacks of peripheral angioedema and abdominal pain without evidence of exposure to an allergen or in the context of a family history of similar conditions. The diagnosis

can be confirmed by testing C1EI activity in blood. Indirect measures of reduced C1EI activity such as low C2 and C4 levels will be seen in all subtypes of HAE. Direct immunohistochemical quantification of C1EI will confirm a deficiency such as seen in type 1, but normal to elevated levels in type 2 and 3. A functional test of C1EI activity (measured as a fraction of normal activity) will show significantly reduced activity in all forms of HAE and in practical terms is the most useful test because it is specific for the disorder and will be reduced in all subtypes.¹⁻³

Long-term treatment for this condition includes the use of antifibrinolytics such as *ε*-aminocaproic acid (EACA) or tranexamic acid, substituted androgens (e.g., methyltestosterone, fluoxymesterone, oxymetholone), synthetic androgens (e.g., danazol, stanozolol) or fresh frozen plasma (FFP) transfusions.^{1,2,5} For acute attacks or short-term prophylaxis, fresh frozen plasma (FFP), C1EI, or the kallikrein inhibitor aprotinin have been used. C1EI is currently recommended as prophylaxis for surgery or any anaesthetic procedure.^{1,2,5} Fresh frozen plasma may also be given but can precipitate attacks because of the complement component of the infusion.^{1,2,5} Further management measures include decreasing estrogen intake and maintaining good dental health.² Commonly used medications for other forms of angioedema (antihistamines, steroids, epinephrine) are not effective in HAE.^{1,2,5}

Several issues complicate the management of HAE during pregnancy. The effect of pregnancy on HAE seems variable, as reports claim that the condition may get better or worse with pregnancy.²⁻⁶ There is a limited number of case reports of HAE in pregnancy,⁵⁻¹² so management suggestions are based on expert opinion. HAE itself has never been associated with any congenital anomalies.⁵ It is currently recommended that all prophylactic treatments should be stopped because of possible teratogenicity, but if prophylaxis in pregnancy is required the theoretical treatment options include tranexamic acid, EACA, or FFP,^{2,13} with C1EI being reserved for acute attacks.^{2,7,13} Termination of pregnancy is an option.¹¹ Prophylactic C1EI should be given under conditions of physical stress such as labour or surgery.² A multidisciplinary approach to management is warranted.

In the present case, prophylactic EACA was considered but not used. The risk of venous thrombosis when using an antifibrinolytic agent in pregnancy argues against its use. In addition, EACA is a class C teratogen.¹⁴ EACA is considered to be less effective than other options, as it does not increase C1EI levels but rather inhibits C1 and plasmin activation, with consequent sparing of C1 inhibitor usage.² Fresh frozen plasma is considered a poor therapeutic option because of (1) the risk of transfusion-related

complications or infections; (2) the relatively small amount of C1EI per unit of FFP, necessitating multiple units given frequently (up to 18 units over 2.5 months in one study⁸); and (3) the volume load imposed upon pregnancy, and hence the theoretical risk of iatrogenic pulmonary edema following multiple unit transfusion. We cautiously elected to try danazol prophylaxis as it was felt to be a superior prophylactic agent. Danazol carries a known teratogenic risk to a female fetus (class X agent¹⁴), but we felt, after careful review of the literature, that the risk would be considerably lower if danazol was given at this gestational age and dosage.

Danzol (50–800 mg/day) appears to be an effective treatment for HAE and is considered superior to EACA and tranexamic acid as it induces an increase in hepatic production of C1EI.^{1,2} There is evidence to suggest that danazol causes masculinization of female fetuses (clitoromegaly, fused labia, urogenital sinus opening at base of clitoris) if used in pregnancy.¹⁴ Reported rates of virilization of female fetuses exposed to danazol in utero have ranged from 17.8% (with daily maternal doses of danazol of 200 mg or more)¹⁵ to 27.8% (with daily maternal doses of 800 mg).¹⁶ Danazol appears to act by inducing a transient block of the activity of 21-mono-oxygenase and 11 β -mono-oxygenase.¹⁷ It has been used to treat thrombocytopenia of pregnancy due to connective tissue disease.¹⁸ There is one reported case of prophylactic danazol use in pregnancy complicated by HAE, but in that case it was used only for prophylaxis in labour.⁶ We felt that the teratogenic risk in this case might be considerably lower than reported. Firstly, the dose of danazol we were to use was lower than the doses reported in cases of fetal virilization. The lowest dose associated with a case of virilization was 200 mg/day.¹⁴ Secondly, virilization has tended to occur when exposure to the medication is prolonged and takes place between about 8 and 18 weeks of pregnancy.¹⁴ We did not begin therapy until the 23rd week of pregnancy, when the fetal genitalia are more developed and possibly less vulnerable to the teratogenic effects. Unfortunately, danazol prophylaxis was not well tolerated by the patient and it was discontinued.

C1EI is a purified human plasma product indicated for acute attacks and long-term prophylaxis of HAE in pregnant women and in children.⁶ The recommended dose is 1000 to 1500 units given intravenously.^{2,7,19} Cox reported a successful outcome of a pregnancy in which C1EI 1000 units was given intravenously at the start of the second stage of labour and another 1000 units at the conclusion of the third stage.⁷ Five days after delivery, the patient had an unexplained attack of abdominal pain that may have been due to an attack of HAE. Prophylactic medication was not used in this case and the fetus was a male. Chappatte and de

Sweit reported successful outcomes in two pregnancies with HAE.⁵ In neither pregnancy was prophylactic medication used, but in one C1EI was used to treat an acute attack at 23 weeks (1000 units) and was then given as prophylaxis after Caesarean section (1500 units).^{2,6} Thus, there is some evidence for its effectiveness and safety in pregnancy. In the present case, we used quantities of C1EI that had not previously been reported in pregnant patients, with no apparent ill effects to mother or fetus.

CONCLUSION

This is the first documented case of an attempt to use danazol as prophylactic antenatal treatment in a pregnancy complicated by multiple acute episodes of HAE. The use of danazol in pregnancy is currently contraindicated, although in doses of less than 200 mg/day and with exposure beginning only after the 20th week of gestation, the teratogenic effects may be minimized. Danazol therapy was discontinued because it was ineffective for this patient, but the exposure did not lead to virilization of a female newborn. This patient, unlike those in other reports, had multiple and frequent episodes of HAE that were managed with multiple treatment courses of C1EI (22 doses prior to delivery) and had a successful outcome of pregnancy. Such extensive use of C1EI in pregnancy has not been previously reported. This combination of therapy succeeded in maintaining a stable pregnancy and the delivery of a normal female neonate. Further documentation of the effects of low-dose danazol in pregnancy is required, as is documentation of the safety and efficacy of C1EI.

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