

Prophylactic Therapy for Hereditary Angioedema



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KEYWORDS

- Prophylaxis • Hereditary angioedema • Androgens • Tranexamic acid
- Progestagens • C1 inhibitor

KEY POINTS

- Androgens are effective prophylactic agents in many patients with hereditary angioedema but are limited by their side effect profile.
- C1 inhibitor has a more favorable tolerability profile but requires intravenous delivery at current licensing and may require dose titration for maximum efficacy.
- Progestagens and tranexamic acid may have a role as prophylaxis; efficacy is inferior to that of androgens but their favorable side effect profiles make them potential options for women and children.
- Short-term prophylaxis should be considered for all procedures, with most evidence for efficacy of C1 inhibitor concentrate.

INTRODUCTION

Given the social, psychological, and financial implications of recurrent angioedema, effective prophylaxis has significant potential in improving attack frequency and severity, and subsequent quality of life.

The aim of prophylaxis is to reduce and, ideally, prevent attacks of angioedema. Interventions therefore are potentially lifelong, while hereditary angioedema (HAE) remains treatable but incurable. Prophylaxis therefore needs to be considered alongside comorbidities, drug interactions, side effects, and patient preference, and may need to be changed as these parameters alter throughout life. Prophylaxis also

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needs to be considered in the context of patient individual factors, including location of nearest emergency department facilities, ease of intravenous (IV) access, and frequency and location of attacks.

WHEN PROPHYLAXIS IS INDICATED

Different guidelines take different approaches to prophylaxis, as outlined in [Table 1](#). Prophylaxis does not guarantee elimination of attacks, so reinforcement of an up-to-date and effective acute attack plan is of paramount importance. Importantly, previous attack patterns, including absence of laryngeal edema, do not necessarily reflect future course.⁵

ATTENUATED ANDROGENS

Efficacy

Early placebo-controlled trials involved small numbers of patients but showed a beneficial effect; in one randomized, double-blind, placebo-controlled trial, 9 patients were treated with either placebo or 200 mg of danazol 3 times a day until 28 days elapsed or an HAE attack occurred, at which point patients crossed over to the other treatment arm. Attacks occurred in 93.6% of placebo courses but 2.2% of danazol courses ($P<.001$).⁶ Another randomized trial assessed 10 mg/d methyltestosterone versus placebo in 4 male patients, with crossover after an attack or 3 months of treatment. After 11.8 months, placebo administration was completed, with 19 attacks, compared with 46 months of androgen therapy, with 4 attacks ($P<.001$).⁷ Furthermore, laryngeal

Table 1 Recent guidelines on indications for long-term prophylaxis in hereditary Angioedema		
Guidelines Source	Year Published	Indications for Long-Term Prophylaxis
Canadian Hereditary Angioedema Guidelines ¹	2014	• On-demand treatment alone does not allow patients to lead healthy and productive lives • Suboptimal efficacy of on-demand treatment to control attack severity and frequency • Also consider: frequency and severity of previous attacks, access to emergency treatment, ability to administer on-demand therapy
World Allergy Organization ²	2012	• All severely symptomatic patients • Also consider disease severity, attack frequency, quality of life, availability of resources, and failure to achieve control with on-demand therapy
US Hereditary Angioedema Association Medical Advisory Board ³	2013	• Consider attack frequency and severity, comorbidities, access to emergency treatment, patient experience and preference
Hereditary Angioedema International Working Group (HAWK) ⁴	2012	Majority opinion: long-term prophylaxis indicated if, in the opinion of the expert physician, the patient cannot achieve adequate benefit from on-demand treatment of attacks Minority opinion: consider if, despite optimum on-demand treatment, patients experience: • >12 moderate to severe attacks per year • >24 d/y affected by HAE

swellings were absent with androgen therapy but 4 episodes occurred during placebo therapy.⁷ A similar beneficial effect is seen with other attenuated androgens, although most evidence is based on danazol therapy.⁸ Small open-label studies have shown reduction in attack frequency with both tibolone and oxymetholone.^{9,10}

Several open-label, prospective case studies have also shown that a minimum effective dose could be found for most patients to significantly reduce attack frequency.^{9–13} One study reported that less than 10% of 141 patients on danazol or stanozolol failed to achieve clinically significant reduction in attacks¹⁴ and, in another retrospective case series of 118 patients, danazol was ineffective in only 5.9%, and reduced attack frequency by 83.8% from 33.3 per year to 5.4 per year.¹⁵ In the patients who did experience breakthrough attacks, reasons included intentional dose reduction, provoking infections or trauma, and interruption of continuous danazol therapy.¹⁵

Side Effects of Attenuated Androgens

A limitation of attenuated androgens is their side effect profile, varying from liver dysfunction and cardiovascular risk factor modification to menstrual irregularities, virilization, mood alterations, and weight gain.⁸ These side effects pose challenges when considering prophylaxis for women, particularly of child-bearing age, as well as children and adolescents. Frequency of adverse effects can be high, with one case series reporting only 21.2% experiencing no adverse effects from danazol.¹⁵ Most evidence relates to danazol, because it has been the most commonly used attenuated androgen.

A Web-based survey of 524 previous or current androgen-using patients with HAE revealed that 59% reported at least moderate weight gain, with other symptoms of anxiety, depression, menstrual abnormalities, virilization, aggression, acne, headaches, and sleep disturbance of at least moderate severity for 1 in 3 patients, although there are limitations with recall bias and a greater proportion of women in both groups.¹⁶

The effects of weight gain and menstrual irregularities were shown to be dose dependent in a case-control trial; this study also documented a significantly higher prevalence of arterial hypertension (25%) in the androgen-treated group compared with the age-matched control group, which had a higher proportion of men ($P = .02$).¹⁶ The average weight gain reported varies between studies from 2.3 to 4.5 kg¹⁷ up to 10 kg.¹⁸ Reports of up to 45 kg have been documented after 1 year of 800 mg of danazol.¹⁵

Virilization is a common side effect and has also been shown to be dose dependent.^{15,19,20} Transient virilization of female neonates exposed to androgen therapy during pregnancy has been reported,²¹ so androgens are not recommended during pregnancy.⁴

Abnormalities in Hepatic Enzymes

Multiple studies show a link between androgen use and increase in hepatic enzyme level, which often reverses on cessation of therapy or dose adjustment^{7,11,12,15,21–23}; however, the clinical significance of these changes is not yet established. Of 118 patients on long-term danazol, 14.4% had abnormalities of liver function tests (aspartate transaminase, alanine transaminase, gamma glutamyl transferase [GGT], alkaline phosphatase), and 5 patients subsequently stopped treatment owing to this.¹⁵ Another retrospective study of 46 patients with HAE on long-term danazol showed that 30.4% at year 5 had increases of at least 1 parameter greater than the upper limit of normal, compared with 21.2% of the control HAE group not on androgen therapy;

however, 4 patients had Gilbert disease, and the slight increase in GGT level has been proposed to be linked to increasing age, questioning the clinical significance of these findings.²² There have also been reports of hepatocyte necrosis with stanozolol.²¹

Liver Neoplasms

There are reports of hepatic neoplasms developing in association with attenuated androgens (mainly danazol); one case series with 46 patients on danazol reported 3 hepatic adenomas and 1 case of multiple benign biliary hamartomas.¹⁵ Another case series of 41 patients on long-term danazol prophylaxis found that 3 out of 11 patients on androgens for more than 10 years developed adenomas.²⁴ At follow-up, 2 of the 3 adenomas spontaneously resolved between 18 to 26 months after drug cessation.²⁵ The concern this highlights is that these latter adenomas occurred at doses of danazol commonly used in current practice (albeit at the upper range of recommended dosage), although duration of treatment also appears to be an important risk factor.

There have been 8 reports of hepatocellular carcinoma (HCC) in patients on long-term danazol,^{26–33} and 4 in the context of HAE.^{26,27,29,30} In 5 cases with details available, histology showed a noncirrhotic background, and alpha fetoprotein level was normal.^{26–30} Therefore, ultrasonography is the preferred screening method, although in one report ultrasonography only 9 months before diagnosis was normal.²⁷ There has also been a case report of hepatocellular focal nodular hyperplasia in a 32-year-old woman on 400 mg/d of danazol for 16 years.³⁴

Other ultrasonography abnormalities are less clearly linked to danazol therapy because they are common findings in the general population; in one retrospective study, ultrasonographic findings included cholelithiasis, hepatomegaly, changes in parenchymal reflectivity, liver cysts, and hemangiomas, with no significant difference between patients on and off androgens.²²

Most studies have shown that there may be dose-dependent increases in hepatic enzyme levels. Current guidelines recommend monitoring these on a 6-monthly basis, alongside alpha fetoprotein and at least annual ultrasonography to assess for the development of hepatic tumors.⁴

Cardiovascular Risks and Lipid Profiles

Androgens have been shown to alter lipid profiles, with an increase in low-density lipoprotein cholesterol (LDL-C) and reduction in high-density lipoprotein cholesterol (HDL-C).^{35,36} Most studies of lipid profiles assess danazol, with only 1 cross-sectional study of stanozolol, showing a reduction in HDL-C but no changes in LDL-C.²⁰

A study of 37 patients with HAE on long-term danazol compared with 2 control groups (27 HAE controls off danazol and 66 age-matched and sex-matched healthy volunteers) showed that patients with HAE on danazol had significantly higher levels of LDL-C and apolipoprotein B-100, and significantly reduced levels of HDL-C and apolipoprotein A-1 (ApoA-1) compared with both control groups. There was no significant difference in total cholesterol and triglycerides, although patients on danazol had significantly greater disease severity.³⁶ A follow-up cross-sectional study showed no significant difference in carotid intima thickness between 25 HAE-positive controls and 20 healthy volunteers, despite the HAE group having higher baseline body mass index, creatinine level, and LDL level, and reduced HDL level compared with both control groups.³⁷

A placebo-controlled crossover trial assessing danazol safety in 15 healthy white male volunteers showed a 23% reduction in HDL-C level, and 21% reduction in ApoA-1 after 4 weeks of 200 mg/d danazol, with no effect on LDL-C level; these effects subsequently normalized in the placebo arm of the crossover trial³⁵ (reversibility

has also been documented in other trials in patients without HAE³⁸). However, the short duration of danazol administration did not reflect the findings in patients with HAE, and it may be that the effects on LDL-C level occur after longer treatment.

What is currently unclear is whether this translates to increased cardiovascular or cerebrovascular risk. There are a few isolated reports of unexpected cardiovascular events during case series,¹⁵ but numbers are too small to identify any statistical significance.⁸ However, this issue does require further investigation.

The effect of attenuated androgens on coagulation parameters is not clear at present; a small crossover trial in 15 healthy volunteers showed no change in fibrinolytic or coagulation profiles after 4 weeks of 200 mg/d danazol compared with placebo.³⁵ Bork and colleagues¹⁵ reported 1 patient with a deep vein thrombosis (DVT) and pulmonary embolism (PE) after 11 months of danazol 200 mg/day, but further details on other risk factors are not elucidated.

Hemorrhagic Cystitis

A potentially underexamined effect of danazol is urinary tract abnormalities; 13 out of 69 patients in a 9-year follow-up on long-term danazol developed hematuria, 10 with hemorrhagic cystitis, seen macroscopically as nonspecific erythema with neovascularity and submucosal telangiectasia. Clinical presentation varied from microscopic hematuria (9 out of 69), macroscopic hematuria (1 out of 69) and irritative bladder symptoms (2 out of 69). In all but 1 patient the changes were reversible on cessation of danazol therapy.³⁹

Current Guidelines for the Use of Androgen Therapy as Prophylaxis

Although there are few randomized, double-blinded, placebo-controlled trials, there remains significant evidence that, in a large proportion of patients, attenuated androgen therapy is likely to have a beneficial effect. However, this must be counterbalanced with its significant side effect profile. There has been a gradual reduction in use of androgens as prophylaxis, and doses are not recommended to exceed 2 mg/d for stanozolol, and 200 mg/d for danazol.^{2,40} Current guidelines recommend 6-monthly clinical review with complete peripheral blood count, liver enzyme levels, lipid profile, alpha fetoprotein level, and annual abdominal ultrasonography in order to monitor these risks.⁴

C1-INHIBITOR

Plasma-derived C1-inhibitor (C1-INH) concentrates are increasingly used as prophylaxis for patients with HAE. At present, only 1 formulation, Cinryze, is licensed for prophylaxis, and although administration is IV it has rapidly become a significant option in long-term prophylaxis. Recent data has also demonstrated the efficacy of subcutaneous C1-INH, which is likely to be an important future management strategy.⁴¹

Efficacy

Randomized controlled trials for C1-INH are sparse and include small numbers of patients. A double-blinded, randomized controlled trial showed a positive effect of C1-INH prophylaxis in 6 patients (4 still on androgen therapy). Over 17 days they were given either 5 doses of IV placebo or C1-INH (25 plasma units per kilogram) and crossed over after a minimum 3-week washout period. During C1-INH administration there was greater than a 60% reduction in mean daily scores for peripheral, genital, laryngeal, and abdominal attacks.⁴² Another randomized, double-blinded, placebo-controlled crossover trial allocated 22 patients with HAE to either 12 weeks of IV C1-INH 1000 units twice weekly or placebo (normal saline). Other prophylactic agents

were continued through the trial. IV C1-INH reduced attack frequency over the 12-week period from 12.73 to 6.36 ($P < .001$), significantly reducing severity and duration of breakthrough attacks.⁴³

Subsequent case series^{44,45} and larger open-label trials have supported these earlier findings⁴⁶; one large, multicenter, open-label trial of 146 patients receiving 1000 units of C1-INH every 3 to 7 days showed a reduction in attack frequency to 0.19 attacks per month from a historical attack frequency (retrospectively collected) of 3 per month (a 93.7% reduction; $P < .001$). This study also showed a direct correlation between dosing intervals and attack frequency, and that twice weekly dosing had a more favorable response rate compared with weekly dosing.⁴⁶ There has also been a study showing that weekly 50 units/kg recombinant C1-INH reduced attack frequency from 0.9 to 0.4 attacks per week (95% confidence interval [CI], 0.28–0.56),⁴⁷ which is surprising owing to its shorter circulating half-life than plasma-derived C1-INH.

C1-INH as prophylaxis has been investigated in pediatrics owing to contraindications with androgen therapy. In one crossover, randomized, placebo-controlled trial with 4 children aged 9 to 17 years receiving 1000 units IV C1-INH every 3 to 4 days for 12 weeks, there was a reduction in mean number of attacks from 13 to 7. Subsequently 23 children went on to open-label prophylaxis, which reduced the median monthly attack rate from 3 to 0.39.⁴⁸

A retrospective analysis of clinical trial and compassionate use data during pregnancy showed no drug-related adverse fetal events in the acute and prophylactic use of C1-INH,⁴⁹ which seems to be safe and efficacious.^{50,51} C1-INH is currently the treatment of choice if long-term prophylactic treatment is needed during pregnancy or breastfeeding.⁵²

Dosing and Delivery Route

Cinryze is currently licensed for long-term prophylaxis for HAE at a dose of 1000 units intravenously every 3 or 4 days, with observational evidence supporting the safety and efficacy of home IV infusions by patients⁵³; however, prophylaxis may also be delivered by caregivers and medical or nursing agencies.

Ongoing Developments

One study has shown that escalating doses up to 2500 units every 3 to 4 days was effective and well tolerated in patients who were poorly controlled on 1000 units twice weekly.⁴⁴ There is also a recently published Phase III double-blind randomized control crossover trial of subcutaneous C1 inhibitor showing higher efficacy compared with historical IV regimens in reducing the number of attacks per month. At the time of writing, the approved dose has yet to be agreed. However, early indications are that trough C1-INH function level correlates strongly with likelihood of angioedema attack. Therefore individual trough-based dose adjustment may enable freedom from attacks for the majority.⁴¹

Side Effects

Compared with attenuated androgens, C1-INH is well tolerated, as documented by clinical trials assessing its efficacy and safety; in a trial of 22 patients, 3 adverse events were documented that were possibly drug related: fever, pruritus and rash, and light-headedness.⁴³ In a pediatric study, 3 adverse events of mild severity were reported: fever, headache and nausea, and infusion site erythema.⁴⁸ Large-scale registry and observational data support its high tolerability, with the Berinert Registry reporting a rate of 0.09 events per infusion.⁵⁴

Thromboembolic Events

There have been multiple case reports of thromboembolic events during studies of C1-INH. In an open-label trial of 146 patients, 5 subjects (all with underlying risk factors) experienced thromboembolic events (myocardial infarction, Deep Vein Thrombosis (DVT), 2 cardiovascular accidents, and a pulmonary embolism (PE)); however, none were considered drug related.⁴⁶ Although observational data has not clearly documented an increased risk in thrombosis,⁵⁴ a physician survey of patients on C1-INH and adverse events noted that 18% (3 out of 17) of patients with a central catheter experienced a thromboembolic event compared with 0.6% of patients without a central catheter.⁴⁹ Recent data published from the Berinert Registry reported 2 thrombotic events in 296 subjects and 9148 infusions between 2010 and 2014: 1 myocardial infarction with multiple risk factors thought to be unrelated to C1-INH, and a subclavian DVT in association with an indwelling catheter, giving a total thrombotic event rate of 0.0002 events per infusion.⁵⁵ Caution is therefore needed in patients with preexisting prothrombotic risk factors.

Theoretic Viral/Prion Risk

Being derived from human plasma, there is the theoretical risk of blood-borne virus transmission, along with prions; however, to date there is no documented viral transmission risk, or development of neutralizing antibodies.⁵⁶

TRANEXAMIC ACID

Tranexamic acid (TXA) has been used as a prophylactic agent in the past; its efficacy is lower than that of attenuated androgens⁵ but its more favorable side effect profile has created a role for its management, predominantly in pediatrics.⁴⁰

There are very few trials of TXA efficacy; early trials seemed to show a moderate effect that has not been corroborated on larger-scale data.^{57,58} Sheffer and colleagues⁵⁷ conducted a short, randomized, double-blind, placebo-controlled crossover trial in 18 patients receiving either 1 g of TXA or placebo 3 times per day. Six patients failed to enter the crossover period, but, for those who did, TXA significantly reduced attack frequency (20 attacks over 88 months for TXA and 57 attacks over 53 months with placebo; $P < .005$). In a retrospective case series of more than 400 Italian patients, with a subgroup on prophylactic antifibrinolytics (number not specified), TXA only caused significant attack reduction in 25%, with no effect on a further 45%, and more significant improvements being seen with androgen therapy.¹⁴

Safety Profile and Side Effects

The tolerability and side effect profile of TXA is much better compared with attenuated androgens; common side effects reported include gastrointestinal upset (diarrhea, nausea, and vomiting).⁵⁹ There is a theoretic risk of thrombosis, and case reports exist of patients experiencing thrombotic events while on TXA, albeit in association with other risk factors.⁶⁰ However, there are no reported increased risks of thromboembolic events, including myocardial infarction and stroke, in large trials and meta-analyses in multiple different clinical contexts (cardiovascular surgery, trauma, obstetrics).⁶¹ Caution is advised in patients who have other risk factors for thrombosis.

Current consensus guidelines do not recommend TXA as first-line prophylaxis, owing to inferior efficacy compared with androgens.^{4,62} However, because androgens are contraindicated in the pediatric population, guidelines state that TXA should be considered as first-line prophylaxis, at 20 to 50 mg/kg in 2 to 3 divided doses 'UP TO A MAXIMUM OF 3-6g/DAY', provided there is no personal or family history of

thromboembolism.⁶³ Current guidelines for HAE in women highlight that TXA has been shown to cross the placenta, but there are data reporting no adverse events with its use in the second and third trimesters, although treatment was for shorter duration than is typically seen in the HAE population. Cases therefore need to be considered on an individual basis with discussion of risks and benefits.⁵² TXA has been shown to be present in breast milk and therefore should be stopped during breastfeeding.⁶⁴

PROGESTAGENS

Hormonal influences on disease expression of HAE are well established, with one study reporting a worsening of attack frequency at puberty in 62% of 150 women surveyed.⁶⁵ Menstruation triggered attacks in 35%, and ovulation in 14%.⁶⁵ Estrogens and combined oral contraceptives typically worsen disease for women and should be avoided.⁶⁵

Although there are no randomized controlled trials assessing progestagens as prophylaxis, there are observational data supporting its favorable profile as a contraceptive agent in HAE. One retrospective study in a French cohort of 55 female patients with HAE types 1 to 3 and idiopathic angioedema showed a benefit of oral progestins. Of those on progestin-only pills (POPs), 61.3% had an improvement in symptoms compared with 89.5% of those on the antagonodotrophic progestagens lynestrenol, nomegestrol acetate, and chlormadinone acetate ($P = .013$).⁶⁶ However, there was a paradoxical worsening of symptoms in 7 patients in the POP group (on desogestrel, levonorgestrel, and L-norgestrel intrauterine device), which may be from induction of luteal cysts with estrogen production.⁶⁷ A retrospective study reported similar rates of success with POPs, with 64% of patients experiencing symptomatic improvement.⁶⁵

Side Effect Profile

Progestagens are typically better tolerated compared with attenuated androgens; however, some androgenic adverse effects can be noted. In Saule and colleagues'⁶⁶ study, 30.9% of patients reported mild adverse events, mainly weight gain, symptoms of estrogen deficiency, breakthrough vaginal bleeding, and hyperandrogenism, although these largely resolved on switching to an alternative progestagen.

Use as Prophylaxis

There is a role for progestagens as long-term prophylaxis, either as POPs or as high-dose progestins (eg, 10 mg of norethisterone), but their efficacy is likely inferior to androgens and C1-INH. Owing to some androgenic side effects, they are not recommended in conjunction with attenuated androgens to avoid theoretic amplification of adverse effects. Similarly, they should not be combined with TXA owing to theoretic thrombotic risk,⁵² although a recent systematic review reports no increased risk of thrombosis in oral progesterone-only contraceptives, with some limited evidence for possible increased venous thromboembolism risk with injectable progestones.⁶⁸

SHORT-TERM PROPHYLAXIS

Introduction

Aside from a robust acute attack management plan and long-term prophylaxis if indicated, short-term prophylaxis (STP) is an important aspect of prevention and treatment in patients with HAE. It should be considered during any exposure known to increase attack risk. Such exposures include medical, dental, and surgical procedures; patient-specific events that may trigger swelling, such as stress related to examinations; or events in which swelling may incur extra risk, such as adventure holidays.

Dental procedures and upper airway manipulation have been the focus of attention, owing to the potentially life-threatening consequences of local edema and airway obstruction. One retrospective analysis of 171 patients undergoing tooth extractions reported an incidence of HAE attacks (facial or laryngeal edema) of 21.5% in patients without prophylaxis,⁶⁹ typically occurring between 1 and 72 hours after the event (mean, 14.3 hours).⁶⁹ One study of different surgical procedures in a German cohort showed risk ranging between 5.7% and 30.5% (CI, 3.5%–35.7%)⁷⁰ so STP should be at least considered in all patients undergoing any procedure.

Options for Short-term Prophylaxis

There are no prospective trial data directly comparing different methods of prophylaxis, making STP choices difficult for clinicians. One retrospective survey of C1-INH, Attenuated androgens (AAs), and TXA reported a statistically significant improvement in number of breakthrough attacks with C1-INH as STP (9%), increasing to 36% with danazol and 50% with TXA.⁷¹

C1 Inhibitor

At present, Cinryze is licensed at a dose of 1000 units within 24 hours of the procedure, and Berinert (another plasma-derived C1-INH) at 1000 units within 6 hours. Retrospective data available on C1-INH as prophylaxis show efficacy, with one trial showing HAE attacks in only 2% (2 out of 91) of various procedures, in which 1000 units were given within the 24 hours before intervention in 96% of the cases (4% were administered different doses).⁷² In the study by Bork and colleagues⁶⁹ of tooth extractions, 16% of patients experienced an attack after prophylaxis of 500 units C1-INH, and 7.5% of patients after 1000 units ($P<.035$). Recent data published from the Berinert Registry on STP reported a low rate of attacks per infusion of 0.04, 0.06, and 0.11 within 1, 2, and 3 days of the procedure respectively, with median doses of 14.6 IU/kg or 1000 units.⁷³ However, data were not available on the procedure done, or on baseline attack rate, and no control group was available.⁷³ Note that, even despite prophylaxis, breakthrough attacks can occur, so availability of on-demand acute treatment is essential.⁶²

Attenuated Androgens

There is very little literature on the efficacy of attenuated androgens as STP; one study of 12 patients reported no attacks on 600 mg danazol per day for 4 days before and after maxillofacial procedures⁷⁴; however, there were no controls and the numbers are likely to be too small to detect any statistical significance. Current recommended dose of danazol is 2.5 to 10 mg/kg (maximum, 600 mg/d) to be taken daily from 5 days before the procedure and continued until 2 to 3 days postprocedure.¹ If already on androgens, patients may increase the dose 50% to 100% (up to maximum 600 mg/d) over a similar time frame.⁴

Tranexamic Acid

TXA is less used as STP; early small studies showing some efficacy during various dental and nondental procedures⁷⁵ have not been reproduced or corroborated. In a retrospective survey of 134 interventions, TXA was the least used STP agent and 3 of the 6 patients on TXA (20–40 mg/kg in 3 divided doses up to a maximum of 3 g) went on to have episodes of edema.⁷¹ Although documented efficacy is limited, TXA is still recommended as an option should no other choice be readily available.¹

There has also been documented use of a bradykinin B2 receptor antagonist as STP for dental extraction with success; however, given its short half-life, the biological rationale is unclear, and it is not currently recommended in guidelines.⁷⁶

SUMMARY

There are a variety of evidence-based options for both long-term prophylaxis and STP, with only indirect comparisons of agents in studies to date.⁷⁷ Each agent has its benefits and drawbacks in the contexts of efficacy, tolerability, inconvenience, and cost, and better, and more numerous, options for children and pregnant women are particularly needed. There are several new agents undergoing further clinical trials at present that are promising in potentially overcoming some of the limitations with agents currently in everyday use.

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