Tranexamic acid

A review of its use in the management of menorrhagia.

Tranexamic acid (Transamin, Cyklokapron, Exacyl, Cyklo-f) is a synthetic lysine derivative that exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation. In a number of small clinical studies in women with idiopathic menorrhagia, tranexamic acid 2-4.5 g/day for 4-7 days reduced menstrual blood loss by 34-59% over 2-3 cycles, significantly more so than placebo, mefenamic acid, flurbiprofen, etamsylate and oral luteal phase norethisterone at clinically relevant dosages.

Intrauterine administration of levonorgestrel 20 mcg/day, however, produced the greatest reduction (96% after 12 months) in blood loss; 44% of patients treated with levonorgestrel developed amenorrhea.

Tranexamic acid 1.5 g three times daily for 5 days also significantly reduced menstrual blood loss in women with intrauterine contraceptive device-associated menorrhagia compared with diclofenac sodium (150 mg in three divided doses on day 1 followed by 25 mg three times daily on days 2-5) or placebo. Tranexamic acid, mefenamic acid, etamsylate, flurbiprofen or diclofenac sodium had no effect on the duration of menses in the studies that reported such data. In a large noncomparative, nonblind, quality-of-life study, 81% of women were satisfied with tranexamic acid 3-6 g/day for 3-4 days/cycle for three cycles, and 94% judged their menstrual blood loss to be ‘decreased’ or ‘strongly decreased’ compared with untreated menstruations.

The most commonly reported drug-related adverse events are gastrointestinal in nature. The total incidence of nausea, vomiting, diarrhoea and dyspepsia in a double-blind study was 12% in patients who received tranexamic acid 1g four times daily for 4 days for two cycles (not significantly different to the incidence in placebo recipients).

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In conclusion, the oral antifibrinolytic drug tranexamic acid is an effective and well tolerated treatment for idiopathic menorrhagia. In clinical trials, tranexamic acid was more effective at reducing menstrual blood loss than mefenamic acid, flurbiprofen, etamsylate and oral luteal phase norethisterone.

Although it was not as effective as intrauterine administration of levonorgestrel, the high incidence of amenorrhoea and adverse events such as intermenstrual bleeding resulting from such treatment may be unacceptable to some patients.

Tranexamic acid (AMCA) is a potent antifibrinolytic drug occurring in two isomeric forms; the antifibrinolytic potency resides in the transisomeric form. The main action of AMCA is blocking of the lysine-binding sites of the plasminogen molecule, which are of importance for the binding to fibrin. This prevents activation of plasminogen by plasminogen activator also absorbed to fibrin. AMCA can be administered orally or intravenously and is excreted into the urine. It enters tissues and fluids in various concentrations and crosses the placenta. There is no evidence of a thrombogenic effect of AMCA, but in accordance with its action, it prolongs dissolution of fibrin deposits already formed. AMCA is a drug of high clinical value for the treatment of bleedings due to both systemic and local fibrinolysis.

Comparative studies of tranexamic acid with epsilon - aminocaproic acid, danazol and combined oral contraceptives, as well as long-term tolerability studies, would help to further define the place of the drug in the treatment of menorrhagia.

Nevertheless, tranexamic acid may be considered as a first-line treatment for the initial management of idiopathic menorrhagia, especially for patients in whom hormonal treatment is either not recommended or not wanted.

Topically applied antifibrinolytic drugs may be of value in the control of bleeding in active ulcerative colitis. Any impairment of systemic
fibrinolysis in this condition, however, is potentially harmful. Since pharmacokinetic data after the rectal administration of tranexamic acid are non-existent, plasma concentration and recovery in the urine were recorded after a single dose of 2 g tranexamic acid given rectally to five patients with ulcerative colitis and to five healthy volunteers. The plasma concentrations and recovery in the urine that were observed in the patients and volunteers were low compared with those seen after oral intake of the same dose. The plasma concentrations did not reach levels that were considered liable to impair systemic fibrinolysis.

Fetal Risk Summary

This haemostatic agent, a competitive inhibitor of plasminogen activation, is used to reduce or prevent hemorrhage in hemophilia and in other bleeding disorders. The drug blocks the action of plasminogen activators (e.g., tissue plasminogen activator [alteplase; t-PA], streptokinase, and urokinase) by inhibiting the conversion of plasminogen to plasmin. No adverse fetal effects were observed in reproductive toxicity testing in mice, rats, and rabbits. Both Schardein and Shepard cited a 1971 study in which doses up to 1500 mg/kg/day were given to mice and rats during organogenesis without causing adverse fetal effects.

Tranexamic acid crosses the human placenta to the fetus. Twelve women were given an IV dose of 10 mg/kg just before cesarean section. Cord serum and maternal blood samples were drawn immediately following delivery, a mean of 13 minutes after the dose of tranexamic acid. The mean drug concentrations in the cord and maternal serum were 19 g/mL (range <431 g/mL) and 26 g/mL (range 1053 g/mL), respectively, a ratio of 0.7.

Twelve women with vaginal bleeding between 24 and 36 weeks’ gestation were treated with 7-day courses of tranexamic acid, 1 g orally every 8 hours. Additional courses were given if bleeding continued (number of patients with repeat courses not specified).
Four women underwent cesarean section (placenta previa in three, breech in one) and the remainder had vaginal deliveries. One of the newborns was delivered at 30 weeks’ gestation, but the gestational ages of the other newborns were not specified. All of the newborns were alive and well. Two of the mothers were receiving treatment at the time of delivery, and the drug concentrations in the cord blood were 9 and 12 g/mL.

A pregnant woman with fibrinolysis was treated with tranexamic acid and fibrinogen for 64 days until spontaneous delivery of a normal 1400-g girl at 30 weeks’ gestation. No adverse fetal or newborn effects attributable to the drug were reported. Tranexamic acid was used in a woman with abruptio placentae during her third pregnancy. She had a history of two previous pregnancy losses because of the disorder. Treatment with tranexamic acid (1 g IV every 4 hours for 3 days, then 1 g orally 4 times daily) was begun at 26 weeks’ gestation and continued until 33 weeks’ gestation, at which time a cesarean section was performed because of the risk of heavier bleeding. A healthy 1430 g male infant was delivered.

The use of tranexamic acid in a woman with Glanzmann’s thrombasthenia disease was described in an abstract published in 1981. Treatment was started at 24 weeks’ gestation and continued until spontaneous delivery at 42 weeks’ gestation of a healthy boy. A study published in 1980 described the use of tranexamic acid in 73 consecutive cases of abruptio placentae, 6 of which were treated for 112 weeks (10). Six (8.2%) of the newborns were either stillbirths (N=4) or died shortly after delivery (N=2), a markedly reduced mortality rate compared with the expected 33%-37% at that time. None of the deaths were attributed to the drug. No cases of increased hemorrhage, thromboses, or maternal deaths were observed.

Tranexamic acid (4 g/day) was used in a 21-year-old primi gravida at 26 weeks’ gestation for the treatment of vaginal bleeding. She also received terbutaline and betamethasone for premature labor.
Tranexamic acid was administered as a single dose on admission, and 6 days later a 10-day course was initiated for continued bleeding. Acute massive pulmonary embolism occurred at the termination of tranexamic acid, and following 23 days of treatment with heparin and streptokinase, a preterm 1140-g male infant was spontaneously delivered. No adverse effects in the fetus or newborn attributable to the drug therapy were noted.

A retrospective study published in 1993 examined the question of whether tranexamic acid was thrombogenic when administered during pregnancy. Between 19791988 in Sweden, among pregnant women with various bleeding disorders, 256 had been treated with tranexamic acid (mean duration 46 days), whereas 1,846 had not been treated (controls). Two patients (0.78%) in the treated group had pulmonary embolism compared with 4 (0.22%) (3 deep vein thromboses, 1 pulmonary embolism) (odds ratio 3.6, 95% confidence limits 0.717.8) in the control group. In the subgroups of those patients who were delivered by cesarean section (168 treated, 439 controls), the rates of thrombo embolism were 1 (0.60%) and 4 (0.91%) (odds ratio 0.65, 95% confidence limits 0.15.8), respectively.

Thus, no evidence was found indicating that the use of tranexamic acid during gestation was thrombogenic. Although the purpose of this study did not include examining the effects of the therapy on the fetus or newborn, the authors concluded that in the absence of a thrombogenic risk, there was no reason to change the indications for its use during pregnancy.

In summary, no adverse effects attributable to use of tranexamic acid during pregnancy, either in animals or humans, have been reported in the fetus or newborn. The drug crosses the placenta to the fetus, but its reported lack of effect on plasminogen activator activity in the vascular wall (versus its known effect in the peripheral circulation) may protect the fetus and newborn from potential thromboembolic complications.
Breast Feeding Summary

Tranexamic acid is excreted into human milk. One hour after the last dose following a 2-day treatment course in lactating women, the milk concentration of the agent was 1% of the peak serum concentration. In adults, approximately 30% - 50% of an oral dose is absorbed. The amount a nursing infant would absorb is unknown, as is the effect of the small amount of drug present in milk.

Comparison between mefenamic acid and danazol in the treatment of established menorrhagia

Menorrhagia, abnormally heavy or long menstrual periods, can cause iron deficient anemia (a reduction in iron carrying red blood cells). The effectiveness of mefenamic acid (an anti-inflammatory pain killer) and danazol (a drug that suppresses the production of hormones involved in the menstrual cycle) in treating menorrhagia were compared.

Excessive menstrual bleeding was defined as blood loss greater than 80 milliliters (ml). There were 20 patients who received mefenamic acid (500 mg) three times a day for three to five days, and 20 patients who received danazol (100 mg) twice a day for 60 days.

In the patients receiving mefenamic acid, the blood flow was reduced from 160 to 127 ml. In the danazol treated group, the blood flow was reduced from 163 to 65 ml.

Side effects were experienced by 75 percent of the women treated with danazol. These included breast pain, flushes, acne, irritability, headache, nausea, vomiting, muscle pain and reduction in breast size.

Side effects experienced by 30 percent of the women receiving mefenamic acid were nausea, vomiting, abdominal discomfort, diarrhea, headache, dizziness and fluid retention.
Half the patients in both treatment groups said they would continue therapy. Of the patients not willing to continue therapy, nine women in the mefenamic acid group reported lack of efficacy as the reason, whereas eight danazol treated women cited side effects as the major reason for discontinuing therapy.

Although mefenamic acid was less effective, fewer side effects may make this the preferred therapy.

What are the long-term effects of taking tranexamic acid?

In answering this part of the question, we have interpreted long-term to mean a continuous dose over a long period of time or tranexamic acid taken for short duration episodically over a long period. We have also assumed you were interested in just adverse effects rather than beneficial effects. Overall, we found very few studies reporting long-term outcomes.

A Cochrane review on antifibrinolytics, last updated in August 2000, reports:

“There has been a reluctance to prescribe tranexamic acid due to possible side effects of the drugs such as an increased risk of thrombogenic disease (deep venous thrombosis). Long term studies in Sweden, however, have shown that the rate of incidence of thrombosis in women treated with tranexamic acid is comparable with the spontaneous frequency of thrombosis in women.”