

Clinical applications

Inhibitors of fibrinolysis in the treatment of haemophilia

CR RIZZA

From the Oxford Haemophilia Centre, Churchill Hospital, Oxford, England

When Okamoto and his associates began their systematic search in 1947 for a synthetic inhibitor of fibrinolysis they aimed to find a substance of value in clinical conditions in which hyperplasmaemia was significant—conditions such as excessive bleeding associated with prostatic and thoracic surgery and with abruptio placentae. They discovered two potent inhibitors of fibrinolysis, epsilon-aminocaproic acid (EACA)¹ and tranexamic acid (amino-methyl-cyclohexane carboxylic acid) (AMCA).² Both drugs have been used with mixed success in a variety of clinical conditions during the past 20 years. I shall confine myself to their use in treating haemophilia (factor VIII deficiency) or Christmas disease (factor IX deficiency). A third inhibitor of fibrinolysis, aprotinin (Trasylol), prepared from bovine lung is also commercially available. In addition to acting as an inhibitor of plasmin and plasminogen activator it has a weak anticoagulant action. It has been very little used in haemophilia except as an instillation into joints during some forms of joint surgery and will not be discussed.

Epsilon-aminocaproic acid (EACA)

Okamoto and his associates thought that EACA acted by inhibiting plasmin, but Alkjaersig *et al.*³ showed that it was principally a competitive inhibitor of plasminogen activator and acted in this respect *in vivo* at a concentration of 0.1 mmol/l. Higher concentrations of the order of 50 mmol/l were required to inhibit plasmin.

DOSAGE, ABSORPTION, DISTRIBUTION, AND EXCRETION

The drug is rapidly and effectively absorbed from the gastrointestinal tract, and after a single oral dose peak plasma concentrations occur within two hours.⁴ Renal clearance of the compound is high and most of the dose is excreted within 12 hours. For this reason and because absorption from the gut is so

effective administration by mouth is preferable when prolonged action is required. McNicol *et al.*⁴ found that a plasma concentration of 1 mmol/l (13 mg/100 ml) significantly inhibited plasminogen activator and that this concentration could be achieved with a loading dose of 4-6 g by mouth followed by 1 g hourly. Such a regimen is not very practicable in routine use and 0.1 g/kg every 6 hours is probably as effective.

Tranexamic acid (AMCA)

Tranexamic acid is a powerful inhibitor of fibrinolysis and *in vivo* is about twice as active as EACA in this respect.⁵ Like EACA it is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur after 1-2 hours. It is rapidly excreted unchanged in the urine. Effective therapeutic concentrations can be achieved with 10-20 mg/kg three times a day intravenously or by mouth. Compared with EACA it has the advantage that gastrointestinal side effects are very uncommon. Because of that AMCA has largely replaced EACA in treating haemophilic bleeding.

Side effects and toxicity of EACA and AMCA

The most common side effects of EACA are relatively mild and affect mainly the gastrointestinal tract.⁶ By mouth it is particularly liable to cause gastrointestinal effects, including abdominal discomfort, nausea, occasionally vomiting, frequent loose bowel movements, and troublesome borborygmi. Some patients have giddiness and postural hypotension, and we have seen two otherwise fit haemophiliacs taking the drug faint without warning on standing up quickly. Other side effects include myopathy,⁷ an acute delirious state,⁸ and inhibition of ejaculation.⁹ A more serious risk is that of thrombosis.

If it is accepted that the fibrinolytic and coagulation

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processes are in dynamic balance then clearly antifibrinolytic agents may, by reducing fibrin clearance from the blood vessels, predispose to thrombosis. There are now several reports of patients in whom vascular thrombosis has been attributed at least in part to treatment with inhibitors of fibrinolysis.¹⁰⁻¹³ The cases described recently by Ryden and Lundberg¹² were of two healthy young women taking AMCA for menorrhagia. They both developed cerebral thrombosis; both survived. The case described by Davies and Howell¹³ was that of a woman taking AMCA for hereditary angioneurotic oedema. She suffered carotid artery thrombosis and cerebral infarction, from which she died.

Use in haemophilia

The use of inhibitors of fibrinolysis in the management of haemophilia has slowly evolved over the past 20 years. It probably dates from the observation of Boudreaux and Frampton¹⁴ that the ingestion of peanuts was effective in reducing haemorrhage in haemophilia. Boudreaux, who himself suffered from Christmas disease, noted that a haemarthrosis of his knee rapidly improved after he had eaten a 'large handful of roasted peanuts'. He also showed that the active principle was present in an alcohol extract of peanuts. From further work, using hamsters, he suggested that peanuts might contain a vasoconstrictive agent. Later others showed that an alcohol extract of peanuts contained an inhibitor of fibrinolysis and other proteases.¹⁵

There followed several reports of the use of peanuts or various extracts of peanuts in the management of haemophilia, mostly in uncontrolled studies. In 1967 Verstraete and Ruys¹⁶ reported a controlled trial in which they found no benefit from the ingestion of peanuts or extracts of peanuts. Despite this, the idea that increased fibrinolysis might be important in haemophilia persisted, and numerous investigations have been made of the effect of epsilon-aminocaproic acid or tranexamic acid in bleeding in haemophilia.

Antifibrinolytic drugs have been used in haemophilia mainly in three ways: (1) for treating haematuria, (2) as prophylactic agents to prevent bleeding into joints and muscles, (3) in dental and other forms of surgery.

HAEMATURIA

Haematuria is probably the third most common type of bleeding seen in severe haemophiliacs. In most cases no cause is found and trauma does not seem to play a part. Treatment with even large doses of the appropriate clotting factor often fails to control haemorrhage and this has led to the use of

other forms of treatment such as antifibrinolytic agents or corticosteroids. The rationale for the use of inhibitors of fibrinolysis was to try to counter the effect of urokinase, the naturally occurring plasminogen activator present in urine, and thereby obtain haemostasis by preventing lysis of fibrin clots.

McNicol and his colleagues¹⁷ were probably the first to report the use of EACA in a haemophiliac with haematuria. The haematuria stopped but the patient subsequently developed renal colic due to ureteric obstruction by clot. Further reports followed of EACA controlling haematuria^{18,19} but the incidence of clot colic and renal obstruction was high.²⁰⁻²³ A recent review²⁴ noted that out of 66 haemophiliacs given EACA for haematuria 52 improved, 14 were unchanged, and 10 showed signs of renal obstruction by clots. The obstruction had cleared in most by 3-4 months, but the patient reported by Gobbi²² had bilateral obstruction and died.

Clot obstruction of the renal tract, however, is not infrequent in haemophiliacs with haematuria and may occur in patients who have received no factor VIII replacement as well as in those who have been given factor VIII with or without antifibrinolytic therapy. It is therefore difficult to know how much EACA or AMCA contributed to the renal obstruction in the reported cases. Nevertheless, renal obstruction is potentially so dangerous that any drug which might add to the risk of it should not be used. It is now generally agreed that EACA and AMCA are contraindicated in haemophiliacs suffering from haematuria, especially severe haematuria.

PROPHYLAXIS

Many have reported on the use of antifibrinolytic agents in the prophylactic treatment of haemophilia. Abe and his associates²⁵ described considerable clinical improvement in two patients taking EACA, and Mainwaring and Keidan²⁶ reported subjective improvement in five out of six children treated for three months with EACA compared with a similar period with no treatment. Reid and his colleagues,²⁷ who gave EACA to 17 severely affected haemophiliacs over periods ranging from 2-16 months, claimed that the patients benefited. There was a statistically significant reduction in the number of haemorrhages, number of transfusions required, time spent in hospital, and time lost from work. Also, rather interestingly, the partial thromboplastin time, Hicks-Pitney screening test, and prothrombin consumption tests all improved towards the normal. All these reports can be criticised on grounds of design of the study, criteria used for assessing benefit, and the possibility of observer bias.

Two controlled trials of EACA^{28,29} and two of AMCA^{30,31} have been carried out in haemophiliacs.

Gorden *et al*²⁸ studied 10 severely affected patients during three periods, each of six weeks, when the patients took EACA, placebo, or no treatment. Although a reduced incidence of spontaneous bleeding while on EACA just failed to be statistically significant the number of spontaneous haemorrhages was half that while on placebo and suggested an important treatment effect. Strauss and his associates²⁹ gave eight severely affected patients EACA or a placebo on alternate months for 8-13 months. There was no improvement in the number of bleeds or the number of admissions to hospital. Bennett, Ingram, and English³⁰ gave AMCA or placebo to 13 haemophiliacs and found that the effect of AMCA on the incidence of bleeding was minimal and the need for factor VIII transfusion was not reduced. They concluded that there was no satisfactory evidence on which to recommend EACA or AMCA for prophylaxis in haemophilia.

Rainsford and his associates³¹ carried out a double-blind cross-over study of AMCA or placebo in 20 haemophilic boys attending a residential school for handicapped children. The study was carried out over two school terms and had the advantage that the boys were closely supervised and all haemorrhages were carefully documented. The results showed a significant reduction in the number of spontaneous bleeding episodes while on AMCA.

In summary, the weight of published evidence suggests that EACA and AMCA have no significant effect in the prophylactic treatment of haemophilia. Nevertheless, the work of Rainsford *et al.* and Gordon *et al.* show that more extensive studies would be justified.

DENTAL EXTRACTIONS

EACA has been used since 1964 for the management of haemophiliacs undergoing dental extraction. The rationale of its use is to inhibit the local fibrinolytic activity in the tissues and saliva which contributes to lysis of clots in the tooth sockets 2-3 days after operation. EACA was given before and after extraction in 11 haemophiliacs for the removal of a total of 31 teeth.³² Apart from careful packing of the sockets and protecting the gums no other treatment was given. No transfusions were given at the time of operation and none was required afterwards. Similar results were reported by Cooksey, Perry, and Raper³³ who found that EACA therapy along with suturing the sockets produced more adequate haemostasis than the conventional transfusion combined with local measures. Tavenner³⁴ used EACA in 61 dental extractions and found that, compared with the period before 1964 when he did not use EACA, the average time in hospital and the amount of transfusion required was reduced.

Although it was difficult to make an accurate assessment, EACA seemed to him to be of undoubted value.

In a double-blind study³⁵ 31 patients having dental extractions were given enough factor VIII or IX immediately before surgery to raise their factor concentration to 50% of normal. At the same time they also received EACA 6 g or placebo intravenously followed by EACA 6 g or placebo 6-hourly for 7-10 days. All patients also received penicillin or erythromycin to control oral infection. Bleeding from tooth sockets occurred in all except one of the 12 control patients on 46 out of a possible 132 days. In the EACA treatment group three out of 11 patients bled. Seven of the 12 control patients required postoperative treatment whereas only one of the 11 patients in the EACA group bled enough to need attention. This study showed conclusively that EACA is a useful adjunct to transfusion therapy and saves factor VIII or factor IX.

Similar results were obtained by Forbes and his associates³⁶ with AMCA in haemophiliacs undergoing dental extraction. In a double-blind study 28 patients received a transfusion of factor VIII or IX equivalent to 1000 ml plasma and 1 g AMCA or placebo three times a day for five days. Blood loss was measured by ⁵¹Cr-labelled red cells. It was significantly reduced in patients receiving AMCA compared with the placebo group. There seems little doubt now that both EACA and AMCA have a part to play in dental extractions in haemophiliacs, but because of its lack of side effects AMCA has largely superseded EACA and is probably the drug of choice.

Oral bleeding apart from that from dental extraction is common in young haemophiliacs, usually from injury to the tongue or fraenum. Because the bleeding is often insignificant and because of the distress often caused by venepuncture and transfusion many doctors give inhibitors of fibrinolysis either alone or with a single dose of factor VIII or IX in these cases. Corrigan³⁷ successfully used combined EACA and factor replacement therapy in 10 haemophilic children with bleeding from the mouth not associated with dental extraction. His regimen was a single dose of cryoprecipitate (2 bags/10 kg body weight) followed by EACA 6-hourly for five days. In all cases bleeding stopped within one hour and no further replacement therapy was required.

OTHER FORMS OF SURGERY

Inhibitors of fibrinolysis have been found to be of value in haemophilic patients undergoing synovectomy.³⁸ By instilling Trasylol into the joint and giving EACA systemically at the time of operation successful synovectomies were carried out on 43

patients. The patients were also given fresh frozen plasma (18-20 ml/kg) or cryoprecipitate for six days. No patient bled on this regimen. The same combined therapy was used to treat haemophiliacs undergoing other forms of orthopaedic surgery such as arthrodesis and tendon lengthening.³⁸ A total of 16 operations were carried out without bleeding complications.

The place of inhibitors of fibrinolysis in other forms of surgery in haemophilic patients is not clear. We have avoided using them for thoracic or abdominal surgery for fear that any haemorrhage into the closed cavities might result in troublesome insoluble clots. On the other hand, we have used EACA and, more recently, AMCA along with factor VIII replacement for operations such as repair of inguinal hernia, haemorrhoidectomy, stripping of varicose veins, adenotonsillectomy, and other superficial operations as well as for orthopaedic operations.

Because of the hypocoagulable state in haemophilia one would expect arterial or venous thrombosis, the most important complication of antifibrinolytic therapy, to be less likely in haemophiliacs unless they were at the same time receiving sufficient factor VIII replacement to maintain a normal haemostatic level throughout the day for many days. The position, however, is different in Christmas disease. Some of the factor IX concentrates used in Christmas disease may give rise to thromboembolism not only in patients with liver disease, known to be at high risk, but also in patients suffering from severe Christmas disease. Most reports of this have come from the United States and followed the use of certain commercial preparations of factor IX.³⁹ The factor IX concentrates made by the National Health Service fractionation laboratories seem to carry less risk of causing thromboembolism in patients with Christmas disease.^{40 41} Nevertheless, by their very nature those concentrates are potentially thrombogenic, and this must be taken into account when planning combined therapy with factor IX concentrates and inhibitors of fibrinolysis.

Having said that, I must add that our practice is to use EACA or AMCA in factor IX-deficient patients in the same way as we do in those deficient in factor VIII. So far we have not seen any thromboembolic complications with combined factor IX and antifibrinolytic therapy even in patients undergoing total hip replacement and requiring factor IX replacement for 2-3 weeks.

Conclusion

Epsilon-aminocaproic acid and tranexamic acid are both of value in haemophiliacs undergoing dental

surgery, and their use has resulted in a considerable saving of coagulation factor concentrates at the time of operation. Three out of four controlled trials of their use in the prophylactic treatment of spontaneous bleeding in haemophilia have failed to show that they significantly reduce the number or severity of bleeds. Nevertheless, one of the trials did show some reduction in the incidence of bleeding, and further studies would be justified. EACA and AMCA both seem to be effective in the control of haematuria in haemophilia either when given alone or with conventional coagulation factor therapy. But the risk of renal tract obstruction is so high that it is probably wiser to treat the haematuria by other means.

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