PAPERS AND ORIGINALS

Tranexamic Acid in Control of Haemorrhage after Dental Extraction in Haemophilia and Christmas Disease

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Summary

In a double-blind trial tranexamic acid (AMCA, Cyclokapron), 1 g three times a day for five days, significantly reduced blood loss and transfusion requirements after dental extraction in patients with haemophilia and Christmas disease. No side effects were seen in either group of patients. Screening tests showed no toxic action of tranexamic acid on the liver, kidney, or heart.

Introduction

Before the advent of plasma replacement therapy the elective removal of teeth from patients with haemophilia or Christmas disease was absolutely contraindicated and often led to death (Legg, 1872). With new concentrates of factor VIII and IX available, however, dental extraction in haemophilia is usually straightforward. The degree of bleeding after extraction varies greatly and depends on the severity of the disease, the type of tooth and the number extracted, and the degree of force required to remove them. Therapy should, if possible, be continued until complete healing of the socket has taken place, and this exposes the patient to the danger of serum hepatitis transmitted from plasma concentrates. A search has therefore been made for agents to reduce or eliminate the need to give plasma. As bleeding from the haemophilic tooth socket is presumably due, in part, to an imbalance between the deposition of fibrin clot and digestion of this clot by the enzymes of the fibrinolytic system, attempts have been made to improve haemostasis by using the antifibrinolytic drug aminocaproic acid (EACA, Epsikapron) (Reid *et al.*, 1964; Cooksey *et al.*, 1966; Tavenner, 1968; Walsh *et al.*, 1971).

Trials of aminocaproic acid have, however, been inadequately controlled, and a wide variety of criteria of efficacy have been used—for example, Cooksey *et al.* (1966) and Tavenner (1968) used transfusion requirements and days spent in hospital, others (Alagille *et al.*, 1965; Marini *et al.*, 1966; Giordano *et al.*, 1967; Paddon, 1967) compared visible blood loss, and some (Reid *et al.*, 1964) used the fall in the haemoglobin level. Walsh *et al.* (1971), in their well-controlled, double-blind trial, used the amount of plasma concentrates as the index of benefit. We describe here a double-blind trial of tranexamic acid (AMCA, Cyclokapron) in dental extraction in patients with haemophilia and Christmas disease in which measurement of the blood loss was carried out with ^{51}Cr-labelled red blood cells. Observations were also made of possible toxic effects of tranexamic acid.

Patients and Methods

Twenty-eight patients aged 13 to 65 years were studied during 32 separate episodes of dental extraction. Twenty patients had classical haemophilia and eight had Christmas disease.

Informed consent was obtained from all the patients or their parents before they were included in the trial. A history of haematuria in the previous four weeks or the presence of red cells in a fresh sample of urine were absolute contraindications to inclusion in the trial.

By means of a double-blind technique and random allocation to the trial the patients received either tranexamic acid (1 g three times a day) or placebo tablets. Therapy was started two hours before extraction and continued for five days.

Blood loss was measured with ^{51}Cr-labelled red cells as described by Watson and Dickson (1964). This entailed separate collections of oral secretions and faeces over 24-hour periods for five days. On day four the patient received a purgative.

Each patient received the factor VIII or IX equivalent of 1,000 ml of human plasma intravenously one hour before extraction and also tetracycline (250 mg four times a day). All extractions were carried out under local anaesthesia, including,

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where appropriate, inferior dental block. No side effects resulting from this procedure were observed in any patient. In the event of excess bleeding from the sockets in the five-day period a clinical decision was made to infuse further blood products. Only sufficient plasma or plasma concentrate to stop the bleeding was given. The clinician did not know the results of the laboratory assays or which tablet the patient was receiving.

Factors VIII and IX were assayed by using the method of Margolis (1958) as modified by Breckenridge and Ratnoff (1962). Tests of fibrinolysis were performed as previously described by McNicol and Douglas (1964), and assessment of criteria of liver and renal function was performed by standard AutoAnalyzer techniques. Haematological indices were measured on the Coulter-S counter and the erythrocyte sedimentation rate (E.S.R.) was determined by the method of Westergren (1920). Inhibitors of factor VIII and IX were sought by using the method of Biggs and Bidwell (1959). Standard 12-lead electrocardiograms were made in all patients before and at the end of the trial.

Details of both groups of patients are given in Table I.

TABLE I—*Clinical Data on Patients receiving Tranexamic Acid and Placebo*

	Placebo	Tranexamic Acid
No. of episodes of extraction	16	16
No. of patients	14	14
No. with haemophilia	9	11
No. with Christmas disease	5	3
Mean (range) level of plasma factor (%)	4·5 (0-22)	5 (0-23)
Clinical severity:		
Severe	7	8
Moderate	6	5
Mild	1	1

TABLE II—*Comparison of Treated and Placebo Groups after Tooth Extraction*

	Placebo	Tranexamic Acid
Mean No. (range) of roots extracted	5·5 (2-12)	6·9 (2-22)
Mean (range) blood loss per patient (ml)	84·1 (4-323)	61·2 (1-749)
Mean (range) blood lost per root extracted (ml)	15·3 (0·5-64)	8·9 (0·5-38·6)
Mean No. (range) of units of replacement therapy per root extracted	617 (0-15,800)	30 and 65 in two patients
Mean fall in haemoglobin (g/100 ml)	1·4	0·3
Mean fall in packed cell volume (%)	5·0	0·9

Results

The data on blood loss are shown in Table II.

Teeth Extracted.—As the amount of bleeding is partly a reflection of the extent of the wound area the number of roots removed was considered rather than the number of teeth removed. The number of roots extracted in the tranexamic acid group (mean 6·9) was not significantly different from that in the placebo group (mean 5·5).

Blood Loss.—The mean volume of blood lost per patient in the placebo group was 84·1 ml and in the tranexamic acid group 61·2 ml. There was a wide range in the total lost per patient. The blood loss per root extracted was 15·3 ml in the placebo group and 8·9 ml in the tranexamic acid group. This corresponded to a mean fall of 1·4 g/100 ml in the haemoglobin level and a 5% fall in packed cell volume in the placebo group, and a fall of 0·3 g/100 ml in haemoglobin and 0·9% in packed cell volume in the tranexamic acid group. When using a rank sum test (Mann-Whitney U test) there was a statistically significant difference in blood loss between the placebo group and the tranexamic acid group ($0·01 < P < 0·025$).

Replacement Therapy (Fig. 1).—In only two patients was it clinically necessary to transfuse plasma or plasma concentrate in the tranexamic acid group after the initial dose. One of these patients had extraction of 22 roots, the largest number in this series. In the placebo group 11 patients required multiple infusions during the five-day trial period and five patients did not require replacement therapy; all these had a mild or moderate degree of defect. The patient requiring the greatest amount of replacement therapy had only a moderate degree of haemophilia and had six roots extracted. He was in the placebo group.

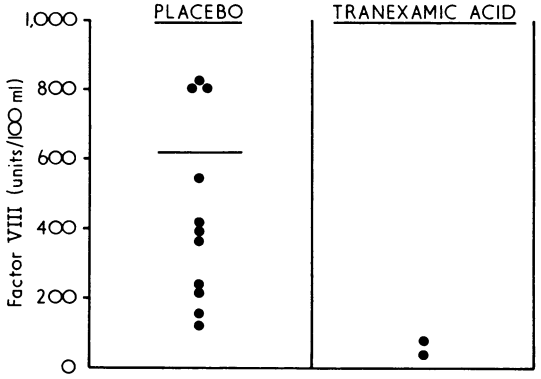

FIG. 1—Number of units of antihaemophilic globulin infused after dental extraction in the tranexamic acid and placebo groups. Results are expressed as units of antihaemophilic globulin per root extracted.

Plasma Fibrinogen Levels and E.S.R. (Fig. 2).—A significant rise in fibrinogen was found in the placebo group on day 5 after extraction. This finding was mirrored in the E.S.R., which was also significantly increased (P 0·05).

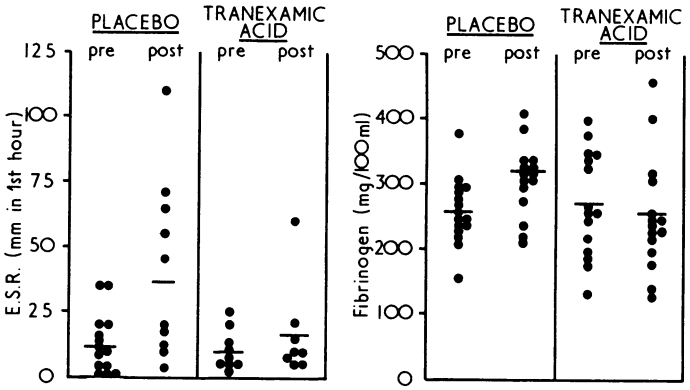

FIG. 2—Changes in E.S.R. in treated and untreated groups. Significant rise in E.S.R. and fibrinogen levels in placebo group is reflection of amount of plasma or concentrate infused.

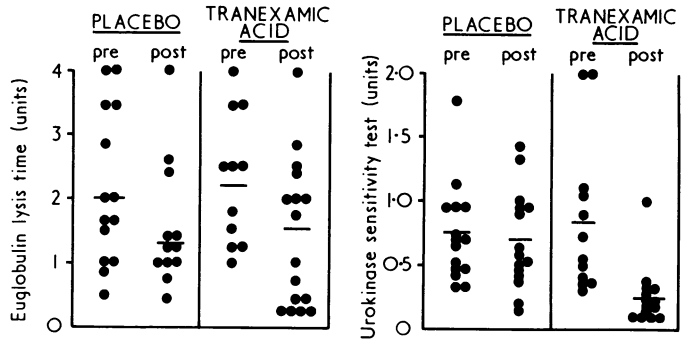

FIG. 3—Depression of urokinase sensitivity test after tranexamic acid indicates that plasma levels were sufficient to inhibit fibrinolysis in this group.

Urokinase Sensitivity and Euglobulin Lysis Time (Fig. 3).—As would be predicted, significant depression of lysis was shown in the urokinase sensitivity test after treatment with tranexamic acid (P 0·05). Both treated and untreated groups showed a fall in the euglobulin lysis times, indicating increased levels of circulating activator. The intergroup results, however, were not significantly different (P 0·1); the tranexamic acid is discarded in the supernatant during preparation of the euglobulin precipitate.

Renal and Liver Function Tests.—Estimations included serum urea, bilirubin, alkaline phosphatase, aspartate transaminase, alanine transferase, and serum albumin and globulin. No significant differences were found between the tranexamic acid and placebo groups. Both groups showed a significant rise in blood urea after extraction (P 0·05).

Electrocardiograms.—No changes were found after therapy in either group.

Side Effects.—No side effects were reported in either group.

Discussion

It has been shown by many authors that surgery can be safely undertaken in haemophilia and Christmas disease if adequate replacement therapy with plasma products is provided. The criteria for success of a new therapeutic agent in dental extraction must include a reduction in blood loss from the extraction site and also a reduction in the total requirement for plasma replacement therapy. The use of tranexamic acid as an adjunct to conventional therapy in this series of dental extraction fulfilled these criteria; both postoperative bleeding and total volume of plasma product required were reduced.

Tranexamic acid is the active trans-stereoisomer of aminomethyl cyclohexane carboxylic acid, and it has been shown by Melander *et al.* (1964) and Okamoto *et al.* (1964) to have powerful antifibrinolytic properties. The molecule has a configuration similar to aminocaproic acid, and as in the case of aminocaproic acid is a competitive inhibitor of plasminogen activation at concentrations in plasma greater than 10^{-4} M and a non-competitive inhibitor of plasmin at concentrations greater than 10^{-2} M. These concentrations may be readily achieved in vivo (Dubber *et al.*, 1965).

Tranexamic acid had the advantage over aminocaproic acid of being between 2 and 20 times more potent (Dubber *et al.*, 1965; Melander *et al.*, 1964; Deutsch and Fischer, 1968) and having minimal side effects. All inhibitors of fibrinolysis when used in patients with haemorrhagic disease have the potential danger of precipitating obstruction of the renal tract with unlysable clots (McNicol *et al.*, 1961; Gobbi, 1967; Van Itterbeek *et al.*, 1968); however, no patients in this study, who were all screened before therapy for the presence of haematuria, showed evidence of this complication.

Although the cause of postextraction bleeding from the tooth socket in the haemophiliac is not clear, it presumably represents an imbalance between defective fibrin formation due to the abnormality in the intrinsic thromboplastin system and the normal removal of deposited fibrin by fibrinolytic enzymes produced by plasminogen activators locally and in the saliva (Albrechtsen *et al.*, 1962). It was noted that all patients in this series showed a fall in the euglobulin lysis times, indicating increased levels of circulating plasminogen activator. This has been recorded by several authors in people under stress (Macfarlane, 1937; Biggs *et al.*, 1947) and may be important in the light of the report by Lucas *et al.* (1962) that extraction of teeth may be safely carried out in haemophiliacs under hypnosis without plasma therapy. In the immediate postextraction period, however, the most important aspect of haemostasis is probably defective fibrin formation.

In a recent study (Walsh *et al.*, 1971) haemophilic patients who had their level of clotting factor raised to 50% of normal by a single haemostatic infusion before extraction rarely bled before the third postoperative day. This suggests that despite the transient nature of the rise in the plasma level of these factors the haemostatic effect is prolonged. Bleeding after three days (up to six days) was commonly seen in the present group of control patients and presumably represented digestion of the haemostatic fibrin plug by fibrinolytic enzymes. Inhibition of these lytic enzymes by tranexamic acid, as was manifested in the prolongation of the urokinase sensitivity tests, allowed fibrin to remain in situ and presumably expedited healing of the sockets. This greatly reduced the necessity to infuse plasma products into these patients.

We feel that measurement of blood loss by means of ^{51}Cr-labelled red cells offers a more accurate assessment of the effectiveness of therapy than fall in haemoglobin or days in hospital. In all patients, however, when bleeding was noted clinically plasma or plasma products were immediately given, and the effectiveness of tranexamic acid must be judged against a combination of total blood lost and the amount of plasma products infused.

There was no evidence of any toxic action of tranexamic acid in this series of patients. There was, however, a significant rise in the mean blood urea levels in both groups after tooth extraction. This probably results from digestion of blood in the gut.

The complications of multiple transfusions are well known (de Gruchy, 1962). In haemophilia these may include production of inhibitors of antihaemophilic globulin and serum hepatitis. It is a reasonable assumption that reduction of plasma requirements by the use of tranexamic acid will reduce the incidence of antihaemophilic globulin inhibitors and serum hepatitis as well as reducing blood loss.

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