Comparison of prothrombin complex concentrate and vitamin K, in oral anticoagulant reversal

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Summary
A randomised clinical trial was undertaken to compare the value of a factor II, IX, and X concentrate (Prothromplex) with intravenous vitamin K\textsubscript{1} (2.5 mg) in reversing an overdose of oral anticoagulants. Rapid partial correction of the prothrombin time, partial thromboplastin time, and the clotting factor assays were observed with the concentrate, but these changes were not always sustained. In contrast vitamin K\textsubscript{1} did not show any great effect at two hours but at 24 hours there was always over-correction despite the conservative dosage, prothrombin times being shorter than the therapeutic range.

The prothrombin complex concentrate provides a quicker, more controlled but less sustained method of reversing the coumarin defect than vitamin K\textsubscript{1}. But there remains a significant risk of hepatits even with a preparation for which strenuous efforts have been made to minimise this risk by screening for hepatitis B virus. The risk should be carefully considered before such concentrates are infused in non-urgent conditions.

Introduction
Clinical experience in British hospitals has shown that patients receiving oral anticoagulant treatment are at particular risk from spontaneous haemorrhage if the British ratio is greater than 5.0. When vitamin K\textsubscript{1} is used to correct this overdosage patients may become relatively haemostatically and possibly resistant to coumarin drugs, which makes their subsequent anticoagulant management difficult. Furthermore, if the patient is suffering life-threatening bleeding more rapid means of correction are required as vitamin K\textsubscript{1} reversal takes some hours to be effective. The development of prothrombin complex concentrates containing vitamin 1-K-dependent clotting factors has offered a possible means of reversing the coumarin defect with small volumes of infuse containing large quantities of clotting factors. A great potential hazard of using these concentrates in patients with recently established thrombosis is, however, the production of disseminated intravascular coagulation (DIC). Reports of the safe use of the concentrates in treating Christmas disease and liver disease has prompted this study, in which the effectiveness of a prothrombin complex concentrate and vitamin K\textsubscript{1} in reversing oral anticoagulant overdosage were compared. A product containing factors II, IX, and X only (Prothromplex-Immun; Serological Products Ltd, Dunton Green, Kent) was studied as it is the type of preparation generally available.

Methods
Eighteen instances of overdoses with nicoumalone (Synthrome) and two with warfarin were studied. Patients with a British ratio over 5.0 were randomised into two groups. Group 1 (nine patients) received 2.5 mg vitamin K\textsubscript{1}, intravenously, while group 2 (nine patients) received the concentrate intravenously over 10 minutes, the doses of concentrate varying from 4.7 to 16 units/kg body weight with a mean dose of 12 units/kg. The concentrate contained 0.01-0.05 IU heparin/unit of factor II. Blood pressure, pulse, and temperature were observed every 15 minutes for one hour after infusion. In both groups blood specimens were taken before and half an hour, two hours, and 24 hours after infusion. No oral anticoagulants were given for 24 hours after infusion.

Laboratory tests—Full blood count; platelet count; measurements of prothrombin time (using British comparative thromboplastin) and partial thromboplastin time (using the proposed international partial thromboplastin time reference preparation); specific assays for factors II, VII, and X; and measurements of thrombin time, fibrinogen, and fibrinogen degradation products (FDP) (by haemagglutination inhibition assay using human red blood cells) were performed on all specimens. Patients receiving the concentrate were screened for the presence of hepatitis B surface antibody (HBsAb) and antigen (HBsAg) before infusion and every month, when possible, for at least six months. (HBsAb and HBsAg were detected by passive haemagglutination.)

Results

PROTHROMBIN TIME

Group 1—All patients receiving vitamin K\textsubscript{1} showed reversal of the anticoagulant defect, but at 30 minutes there was no appreciable...
improvement (fig 1). Only at two hours did a pronounced improvement occur. The 24-hour samples always showed an overcorrection by reducing the prothrombin ratio to 1:2-1:4 (mean 1:3), which is less than the therapeutic range (2-3 ratio).

**Group 2**—With the concentrate, maximum correction was observed in all patients at 30 minutes (fig 1). At 24 hours the reversal was thought to be insufficient in two cases as the ratio was prolonged to 10:0 and 10.5, and further infusion was necessary. At 24 hours only one patient showed a slight overcorrection to a ratio of 1:7, which was less than therapeutic. In the other cases the ratio was restored to the conventional therapeutic range (2-0-3:0) or the relatively safe range of 3:0-3:5.

**PARTIAL THROMBOPLASTIN TIME**

**Group 1**—In all cases the partial thromboplastin time was considerably prolonged (mean time 85 seconds; normal range 38-45 seconds). There was no correction at 30 minutes (mean time 84 seconds) but slight correction at two hours (mean time 68 seconds). At 24 hours the partial thromboplastin time was overcorrected—that is, to normal values—in all but two cases.

**Group 2**—The mean value before treatment was 82 seconds. There was an appreciable correction at 30 minutes (mean time 53 seconds), which was sustained in all but the two patients who required a second infusion. In only two patients was there overcorrection to the normal range.

**FACTOR II**

**Group 1**—There was no appreciable change at 30 minutes but all patients showed a slight rise in activity at two hours, which was more pronounced at 24 hours though the activity was still less than normal.

**Group 2**—There was appreciable correction at 30 minutes, which was sustained at two hours, but in most cases these levels had fallen to below the maximum at 24 hours.

**FACTOR X**

**Group 1**—No correction was apparent at 30 minutes but there was slight correction at two hours. The maximal effect was at 24 hours.

**Group 2**—The maximum correction was at 30 minutes. In one patient who needed a second infusion the factor X level had fallen back to a low level (100\(^{\circ}\)) at 24 hours. In five patients there was a considerable fall in the level 24 hours after infusion.

**FACTOR VII**

**Group 1**—No correction was seen at 30 minutes (fig 2). There was a small rise in activity at two hours, but at 24 hours the activity was less than 100\(^{\circ}\) in only one patient (80\(^{\circ}\)).

**Group 2**—In contrast to the results of the other factor assays there was no rise in activity during the two hours after infusion (fig 2). At 24 hours four patients showed a rise in factor VII levels but in five cases the activity remained very low (1-7\(^{\circ}\)).

**OTHER MEASUREMENTS AND FOLLOW-UP IN GROUP 2**

There was no appreciable change in full blood count, platelet count, thrombin time, FDP, or in the clinical values. Eleven patients were followed up for six months or more and 10 remained negative for HBsAg and HBsAb. The 11th patient died of disseminated carcinoma of the breast soon after the study was started. One patient, however, developed hepatitis eight weeks after infusion (peak aspartate aminotransferase 670 IU/l, peak bilirubin 100 \(\mu\)mol/l (5-9 mg/100 ml), peak alkaline phosphatase 335 IU/l). Liver function later returned to normal. The patient remained HBsAg and HBsAb negative and was followed up for six months after the hepatitis.

**Discussion**

The correction with vitamin K\(_1\) occurred in all cases, but at 30 minutes there was no measurable improvement in the prothrombin or partial thromboplastin times or in the depressed levels of factors II, VII, and X. These results contrast with those in patients who received the concentrate, in whom there was an immediate and maximal effect observed at 30 minutes, except in factor VII activity.

Some correction with vitamin K\(_1\) was apparent two hours after infusion in all the tests, but the maximum correction was at 24 hours. From the standpoint of the prothrombin time on which anticoagulant dosage is based, there was an overcorrection at this time in all cases to ratios of 1.2 to 1.4, which are well below the therapeutic range. At these ratios with the British comparative thromboplastin no anticoagulant protection can be expected. This overcorrection occurred despite the fact that a very conservative dose of vitamin K\(_1\) (2-5 mg) was administered. The use of such small doses has been advocated by several

![Graph](image-url)
Headache after carotid endarterectomy

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Summary

Forty-eight hours after undergoing a successful right carotid endarterectomy a patient complained of headache in and behind the right eye radiating to the temple and forehead. The onset of headache was sudden, and the pain was severe and throbbing. After three weeks of regular four- to eight-hour attacks each day the headaches gradually became less frequent. Two months after operation they had disappeared completely.

Headache as a complication of endarterectomy is rare, but typically it is vascular and subsides spontaneously in one to six months. If a predisposition to migraine were a precipitating factor many more cases would be expected. No possible explanation for headache after carotid prearterectomy can account adequately for its apparent rarity.

References

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Introduction

In 1954 Eastcott et al performed the first successful carotid endarterectomy for carotid stenosis. The operation has since been performed widely, although its indications remain somewhat debatable. The operative mortality rate is now about 1%. Complications include postoperative thrombosis, dissection of the intimal flap, and infarction due to distal thrombosis, embolism, or hypotension. Haemorrhage into the ischaemic hemisphere may occur as a result of luxury perfusion.

Lawson noted recently that 90% of patients with transient ischaemic attacks remained symptom free after endarterectomy. No patients were made worse by surgery and no additional neurological deficits were produced. Only two published reports describe a striking symptom encountered during the postoperative period—intense localised vascular headache. No case has been reported from the UK to the best of my knowledge. In view of the manipulation of the common carotid artery, its adventitia, and the innominate artery, it is perhaps surprising that symptoms directly attributable to the localised vascular trauma have been recorded so rarely.

Case report

A 53-year-old man presented with recurrent episodes of transient left-sided weakness present for two months. These were of sudden

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