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Comparison of prothrombin complex concentrate and vitamin K₁ in oral anticoagulant reversal

D A TABERNER, JEAN M THOMSON, L POLLER

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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 K₁ (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 K₁ 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 K₁. But there remains a significant risk of hepatitis 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 K₁ is used to correct this overdosage patients may become relatively hypercoagulable 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 K₁ reversal takes some hours to be effective. The development of prothrombin complex concentrates con-

taining vitamin 1-K-dependent clotting factors has offered a possible means of reversing the coumarin defect with small volumes of infusate 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 disease¹ and liver disease^{2,3} has prompted this study, in which the effectiveness of a prothrombin complex concentrate and vitamin K₁ in reversing oral anticoagulant overdosage were compared. A product containing factors II, IX, and X only (Prothromplex-Immuno; Serological Products Ltd, Dunton Green, Kent) was studied as it is the type of preparation generally available.⁴

Methods

Eighteen instances of overdoses with nicoumalone (Sinthrome) 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 K₁ 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 K₁ showed reversal of the anticoagulant defect, but at 30 minutes there was no appreciable

WHO Collaborating Centre for Anticoagulant Control Regents,
Department of Haematology, Withington Hospital, Manchester
M20 8LR

D A TABERNER, MRCP, research registrar
JEAN M THOMSON, PHD, principal scientific officer
L POLLER, FRCPATH, MD, consultant haematologist

FIG 1—Comparison of prothrombin time responses to concentrate and vitamin K₁ injection. Both values are given for each of the two patients who needed a second infusion.

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 (16%) 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% in only one patient (80%).

FIG 2—Comparison of factor VII responses to concentrate and vitamin K₁ injection. Some lines are superimposed because values in several patients were the same.

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%).

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 μmol/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 K₁ 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 K₁ 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 K₁ (2.5 mg) was administered. The use of such small doses has been advocated by several

authors,^{5, 6} and our findings therefore support the use of a conservative vitamin K₁ dosage regimen. With the concentrate the correction was more controlled in preventing overcorrection but in two out of 11 instances they were not sufficiently sustained, and the patients needed further infusions at 24 hours.

Similarly the partial thromboplastin times indicated an overcorrection with vitamin K₁. Values in seven out of nine patients were restored to normal, but only after two of the 11 concentrate infusions did this occur. The findings with the prothrombin time and partial thromboplastin time tests were mirrored in the specific clotting assays of II and X.

There was a strong contrast in factor VII assay results. With vitamin K₂ correction was detectable at two hours and maximal at 24 hours, eight of the nine patients being restored to 100% activity or above. There was, on the other hand, no rise two hours after the infusion of concentrate. At 24 hours there was some rise, due presumably simply to anticoagulant withdrawal, but in almost half the patients the level was still very low (1-7%). The precise clinical significance of the persistent depression of factor VII is not certain, the only analogues being congenital deficiency of factor VII, in which the danger level is considered to be 5-10%.⁷ On first principles, therefore, a concentrate containing factor VII seems to be preferable to a VII-poor preparation. It requires clinical confirmation that the concentrate we used will arrest bleeding at these low levels of factor VII activity.

Contrary to reports of the thrombogenic risk of some concentrates⁸⁻¹¹ there was no evidence to suggest DIC with use of the Prothromplex concentrate.

The hepatitis B risk with factor IX concentrates is established,¹² but the magnitude of the risk of non-B hepatitis with these products is not generally realised. Prince¹³ suggested that 20% of post-transfusion hepatitis was unrelated to hepatitis B virus. Thus, even if the risk of hepatitis B was eliminated there

would still be a considerable risk of hepatitis with these products. Even in this small series the possibility of transmission of non-B hepatitis in one patient by this product cannot be excluded.

Hence, this concentrate provides a more rapid and controlled but less sustained means of correcting oral anticoagulant overdose than vitamin K₁, which, even in a dose of 2.5 mg, always tends to overcorrect. Our results suggest that the risk of hepatitis may be significant despite careful screening for HBsAg in the donors, and therefore its use in oral anticoagulant reversal should be limited to correcting life-threatening haemorrhage.

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Headache after carotid endarterectomy

JOHN PEARCE

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Summary

Forty-eight hours after undergoing a successful right carotid endarectomy 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.

Introduction

In 1954 Eastcott *et al*¹ 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%.² 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.

Lawson² 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^{3, 4} 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 carotid sinus, 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