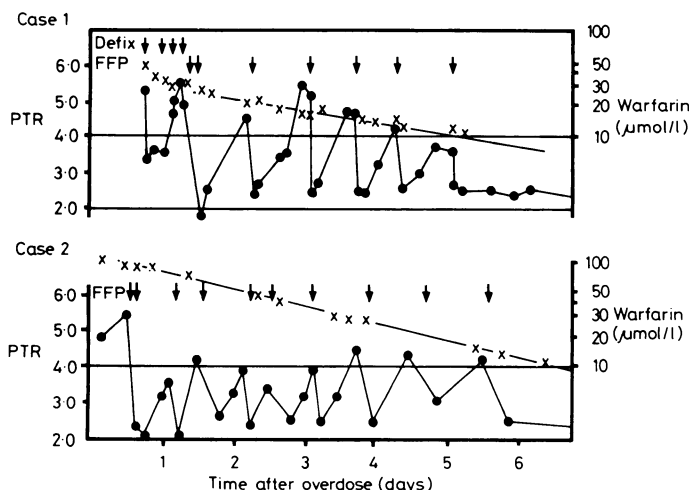


declined with a half life of 80 hours. Fresh frozen plasma was required, as indicated by serial PTR measurements, until the plasma concentration of warfarin and metabolites fell to $10 \mu\text{mol/l}$ ($3.0 \mu\text{g/ml}$). He was then restarted on warfarin after psychiatric and cardiological assessment.

Case 2—A 54-year-old man on long-term warfarin for a prosthetic mitral valve took an overdose of 300 mg of warfarin together with alcohol. Fourteen hours after overdose the PTR was 5.8 (see figure). For six days the PTR was maintained within the therapeutic range by repeated infusions of 300 ml of fresh frozen plasma. The experience gained in case 1 allowed for better control in this patient by more regular administration of fresh frozen plasma at approximately 12-hourly intervals. As in case 1, there was no bleeding. The plasma concentration of warfarin and metabolites on admission was $100 \mu\text{mol/l}$ ($30.7 \mu\text{g/ml}$) and declined with a half life of 45 hours. Again, once the plasma concentration of warfarin had reached $10 \mu\text{mol/l}$ ($3.0 \mu\text{g/ml}$) no further treatment was required, as indicated by the PTR remaining within the therapeutic range. This patient was also restarted on warfarin after psychiatric and cardiological assessment.



Prothrombin time ratio (PTR) and plasma concentration of warfarin and metabolites (PWC) after warfarin overdosage, treated with factor II, IX, and X concentrate (Defix) and fresh frozen plasma (FFP). ● = PTR, X = PWC. The horizontal line represents the upper limit of the therapeutic range of prothrombin time ratio.

Comment

In most cases of massive warfarin poisoning full reversal of anticoagulation is advisable. It is usual to give vitamin K_1 regularly (up to five times daily) until the plasma concentration of warfarin and metabolites has fallen to low therapeutic concentrations.³ Occasionally, as in our patients, there may be a need to maintain therapeutic levels of anticoagulation. In such cases titration of vitamin K_1 is difficult, and anticoagulation may be overcorrected⁴ with doses as low as 2.5 mg vitamin K_1 . Furthermore, the main effect of vitamin K_1 is delayed for several hours.

Administration of clotting factors, however, produces an immediate effect, and is readily titratable against the PTR. Clotting factors may be given as fresh frozen plasma, dried plasma, or freeze-dried concentrates. Dried plasma and freeze-dried concentrates carry a greater risk of hepatitis than low-pool FFP.⁵ Four-factor concentrate (II, VII, IX, X) is not readily available from the Blood Transfusion Service, as the usual method of preparation does not allow the separation of factor VIII from the same donor blood. Three-factor concentrate (II, IX, X) does not have this disadvantage, so it is more readily available and may be effective in reversing overdoses of oral anticoagulants.⁴ Such a concentrate, however, failed to produce adequate reversal in case 1, possibly due to lack of factor VII.⁴

FFP was not required after the plasma concentration of warfarin and metabolites had fallen below $10 \mu\text{mol/l}$ ($3.0 \mu\text{g/ml}$). Although extrapolation of the warfarin elimination curve soon after admission predicted when this would occur, allowance should be made for the wide therapeutic range of warfarin concentrations.

Thus fresh frozen plasma (approximately 12 hourly) is an effective treatment for warfarin poisoning, where complete anticoagulant reversal is undesirable. Estimations of plasma warfarin concentrations enable the approximate duration of therapy to be estimated, but the PTR must be monitored several times daily.

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- Loeliger EA. The optimal therapeutic range in oral anticoagulation. *Thromb Haemostas* 1979;42:1141-52.
- Corn M, Berberich R. Rapid fluorometric assay for plasma warfarin. *Clin Chem* 1967;13:126-31.
- Bjornsson TD, Blaschke TF. Vitamin K_1 disposition and therapy of warfarin overdose. *Lancet* 1978;ii:846-7.
- Taberner DA, Thomson JM, Poller L. Comparison of prothrombin complex concentrate and Vitamin K in oral anticoagulant reversal. *Br Med J* 1976;iii:83-5.
- Wyke RJ, Thornton A, Portmann B, et al. Transmission of non-A non-B hepatitis to chimpanzees by factor IX concentrates after fatal complications in patients with chronic liver disease. *Lancet* 1979;i:520-4.

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Fenbufen-induced erythema multiforme

Fenbufen is a new anti-inflammatory drug, a derivative of propionic acid. Since it was introduced in January 1980 there have been reports of erythematous rashes associated with its use but none of erythema multiforme. We recently saw a patient with erythema multiforme associated with treatment with fenbufen.

Case report

The patient, a 65-year-old woman, had a history of asthma but was not receiving any treatment for this. She had been treated for several years with a thiazide-triamterene combination because of mild hypertension. In July 1980 she was admitted to hospital with a profound systemic illness and a confluent rash. Ten days before admission she had been started on fenbufen 900 mg daily for cervical osteoarthritis. Three days later she had developed a rash, which had begun on her neck and spread to her chest, arms, and legs. Ultimately her whole body was affected except for her face.

On admission she was extremely ill with a temperature of 39°C and a rash typical of erythema multiforme; the mucous membrane was not affected. Results of investigations included erythrocyte sedimentation rate 50 mm in the first hour and white blood cell count $11.8 \times 10^9/\text{l}$ with "left shift." A skin biopsy specimen showed perivascular mononuclear cell infiltration. Blood and urine cultures, chest x-ray examination, and complement fixation tests for *Mycoplasma* and viruses were negative. Routine biochemistry was normal. She was treated with high-dose oral prednisolone (80 mg daily) and made an uncomplicated recovery.

Comment

Twenty-three cases of erythema multiforme associated with non-steroidal anti-inflammatory drugs have been reported to the Committee on Safety of Medicines.¹ This is the first reported case in which this toxic effect has been observed with treatment with fenbufen, but, interestingly, six of the 23 cases occurred in association with ibuprofen, which is also a derivative of propionic acid. As fenbufen is now being widely advertised we wish to alert other doctors to the possibility that patients may develop erythema multiforme as a result of taking this drug.

¹ Committee on Safety of Medicines. *Register of adverse reactions*. London: Committee on Safety of Medicines, 1980.

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