[13] Jacken J, Casaer P, Corbeel L. Valproate, hyperammonaemia, and hyperglycinaemia. *Lancet* 1980;ii:260.
[14] Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child* 1976;**51**:170-9.
[15] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965. Part I. *Arch Dis Child* 1966;**41**:454-71.
[16] Roberts E. Prospectus. In: Glaser GH, Penry JK, Woodbury DM, eds. Anti-epileptic drugs, mechanisms of action. *Adv Neurol* 1980;**27**:484-6.
[17] De Luise M, Blackburn GL, Flier JS. Reduced activity of the red cell sodium-potassium pump in human obesity. *N Engl J Med* 1980;**303**:1017-22.
[18] Lin MH, Romsos DR, Akera T, Leville GA. Na^+ K^+ ATP-ase enzyme units in skeletal muscle from lean and obese mice. *Biochem Biophys Res Commun* 1978;**80**:398-404.
[19] Bondy PK. Metabolic obesity? *N Engl J Med* 1980;**303**:1057-8.
[20] Massey EW, Pellock JM. Meralgia paraesthetica in a child. *J Pediatr* 1978;**93**:325-6.

(*Accepted 25 June 1981*)

SHORT REPORTS

Why request reprints?

It is common practice for original articles in medical journals to give an address for reprint requests. Often authors receive many requests, usually from abroad. Since photocopiers are now freely available in most parts of the world we were interested in the true relevance of reprint requests and canvassed the views of other doctors.

Methods and results

We sent a questionnaire to 280 doctors of grade senior registrar or lecturer and above working in all specialties in the teaching hospitals in Nottingham; 161 replies were received and analysed. The doctors replying included 46 senior registrars and lecturers (31%), 89 consultants and senior lecturers (60%), and 13 professors and readers (9%); 13 did not specify rank. Of these respondents, 57 (35%) published one or no medical papers each year, 87 (54%) published two to five papers, and 17 (11%) published more than five each year. Taking each doctor's estimate together it appeared that nearly 10 800 reprint requests had been received by them in the past year.

The table shows the origin of reprint requests in order of frequency.

Countries of origin of reprint requests (figures are numbers (%) of doctors answering each question)

Answer	North America	Europe	Iron Curtain	Japan, New Zealand, Australia	Third World
Where do your reprint requests come from?					
Most frequently	106 (66)	40 (25)	12 (8)	2 (1)	0
Next most frequently	31 (25)	63 (50)	21 (17)	4 (3)	6 (5)
Do you return reprints on request?					
Occasionally or never	85 (63)	78 (59)	54 (46)	67 (66)	45 (43)
Usually or always	51 (37)	55 (41)	64 (54)	35 (34)	59 (57)

Doctors returned reprints (when available) most often to Iron Curtain and Third World countries, but the response was not high to anywhere. Indeed, only two of the 17 doctors who published more than five papers a year usually returned reprints to North America. Seventy-four doctors (56%) said that any reprints that they had were handed to colleagues locally or remained in a drawer. Reprint requests were regarded as a waste of time and money by 105 doctors (72%), and only 25 (17%) thought that they were a valuable way of keeping in touch with other investigators and knowing who was interested in their work. Nearly a third of doctors thought that reprint requests were a good way of collecting foreign stamps.

When doctors were asked whether they themselves requested reprints from authors 125 (83%) said rarely or never, 19 (13%) said occasionally, and six (4%) said often. When a copy was required 141 (97%) arranged a photocopy locally. Five doctors commented that they requested reprints only when high-quality reproductions of photographs or radiographs were required.

Comment

The large majority of doctors regarded reprint requests as a waste of time and money. Although our questionnaire covered only a small number of doctors, they represented a cross-section from all hospital specialties.

North American and European countries were by far the most common sources of reprint requests, although only a third of doctors usually returned reprints to these countries. It is hard to see any value in requests from these countries, where photocopiers are freely available. Photocopy laws generally allow copies for personal use. The commonly used printed reprint-request postcards (for example, Request a Print), often filled out and signed by secretaries,[1] suggest that requests are accepted practice, especially in North America. The belief that access to library or photocopier facilities may be more difficult in Iron Curtain or Third World countries probably explains the higher return rate of reprints to these areas. It would be interesting to hear how important reprints are to doctors working in these areas.

The estimate of 10 800 reprint requests received by our 161 respondents in the past year suggests that the cost of replying to all requests would be considerable. Assuming return by air mail, postage costs alone would be over £3000. Countrywide, the cost to the National Health Service (which in the end actually pays for the stationery, postage, and time) would be alarming if all doctors replied to every request. Doctors in our area rarely requested reprints themselves from authors, and almost all relied on arranging photocopies of interesting articles locally. Efficient library facilities are a feature of medical centres in most countries.

We do not deny that it is sometimes useful to be able to write to authors about some point of interest or debate, but we believe that reprint requests are largely outdated and a waste of time and money.

We thank our colleagues for completing the questionnaires.

[1] Dirckx JH. Reprints. *N Engl J Med* 1981;**304**:738-9.

City Hospital, Nottingham NG5 1PD
JOHN T MACFARLANE, MA, MRCP, senior medical registrar
MICHAEL H CULLEN, MD, MRCP, senior medical registrar
DAVID C BANKS, MD, FRCP, senior lecturer in therapeutics

Warfarin poisoning in patients with prosthetic heart valves

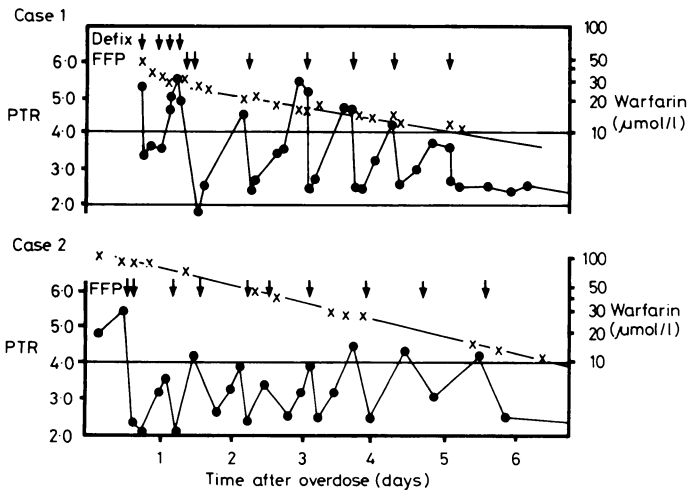
Massive warfarin overdose in patients with prosthetic heart valves requires a prolonged period of carefully controlled partial reversal of anticoagulation. We report two cases where partial reversal was maintained with repeated infusions of fresh frozen plasma. The frequency of treatment was monitored by the prothrombin time ratio (PTR), and serial plasma warfarin concentration estimations predicted the required duration of treatment.

Case reports

Case 1—A 64-year-old man, on long-term warfarin for a Björk-Shiley prosthetic valve, took an overdose of an uncertain quantity of warfarin, digoxin, frusemide, and sedatives. Specific treatment was required only for warfarin. The initial PTR, 18 hours after the overdose, was 5·2 (British comparative thromplastin). The patient was given factor II, IX, and X concentrate (Defix: Scottish National Blood Transfusion Service). When 40 ml of the concentrate had failed to reduce the PTR to within the accepted therapeutic range[1] of 2·0-4·0, he was given repeated infusions of 300 ml of fresh frozen plasma over a period of five days (see figure). This maintained the PTR at or near the therapeutic range. At no time did he bleed. The initial plasma concentration of warfarin and metabolites, measured by fluorimetry,[2] was raised at 44 μmol/l (13·5 μg/ml) (figure) but subsequently

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 μmol/l (3·0 μg/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 μmol/l (30·7 μg/ml) and declined with a half life of 45 hours. Again, once the plasma concentration of warfarin had reached 10 μmol/l (3·0 μg/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 overcorrected[4] 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 μmol/l (3·0 μg/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.

We thank Dr L F Prescott and Dr A T Proudfoot for permission to report patients under their care.

[1] Loeliger EA. The optimal therapeutic range in oral anticoagulation. *Thromb Haemostas* 1979;**42**:1141-52.
[2] Corn M, Berberich R. Rapid fluorometric assay for plasma warfarin. *Clin Chem* 1967;**13**:126-31.
[3] Bjornsson TD, Blaschke TF. Vitamin K_1 disposition and therapy of warfarin overdose. *Lancet* 1978;ii:846-7.
[4] Taberner DA, Thomson JM, Poller L. Comparison of prothrombin complex concentrate and Vitamin K in oral anticoagulant reversal. *Br Med J* 1976;ii:83-5.
[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.

(*Accepted 6 May 1981*)

Royal Infirmary, Edinburgh EH3 9YW
FRANCIS TOOLIS, MRCP, MRCPATH, senior registrar, haematology department (present appointment: clinical research fellow, Blood Transfusion Service, Royal Infirmary, Edinburgh)
R HOWARD ROBSON, MRCP, senior registrar, regional poisoning treatment centre (present appointment: consultant physician, Cumberland Infirmary, Carlisle)
JULIAN A J H CRITCHLEY, PHD, MRCP, senior house officer, regional poisoning treatment centre (present appointment: lecturer, department of therapeutics and clinical pharmacology)

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 $11·8 \times 10^9$/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.

(*Accepted 6 June 1981*)

John Radcliffe Hospital, Headington, Oxford OX3 9DU
ANDREW PEACOCK, MPHIL, MRCP, registrar (now registrar, lung function unit, Brompton Hospital, London SW3)
JOHN LEDINGHAM, DM, FRCP, May reader, Nuffield department of clinical medicine