Postgrad Med J 1999;75:429–430 © The Fellowship of Postgraduate Medicine, 1999

Adverse drug reaction

Quinine-mediated disseminated intravascular coagulation

R K Kedia, A J Wright

Quinine is widely used for the treatment of nocturnal leg cramps and is also commonly present in small quantities in 'bitter' soft drinks. Recognised haematological problems associated with the ingestion of quinine include thrombocytopenia, haemolytic anaemia, neutropenia and disseminated intravascular coagulation (DIC). Five cases of quinine-associated DIC have been reported to date.[1–3] We would like to report a further case which occurred after only two doses of quinine sulphate separated by an interval of 3 months.

Case report

A 79-year-old woman, who was previously fit and healthy, was admitted via Accident and Emergency with a recent onset of multiple bruises, melaena, and hypotension. She was taking bendrofluazide 2.5 mg daily for hypertension. Three months earlier she had complained of leg cramps and had been prescribed quinine sulphate 300 mg as necessary. One dose had been used with good effect at that time.

Two days before admission she had suffered dysuria and frequency of micturition but had received no antibiotic therapy. Leg cramps again became a problem and she took a second dose of quinine sulphate 300 mg. Within 12 hours she had developed spontaneous bruising, haematuria, haemoptysis, melaena, and lightheadedness.

On examination she was fully conscious, pale, afebrile and had multiple ecchymoses on her face, arms and legs (figure). Pulse rate was 90 beats/min, blood pressure 110/60 mmHg lying and 80/60 mmHg sitting. Rectal examination confirmed melaena.

Initial investigations showed haemoglobin 9.6 g/dl, mean corpuscular volume 92.0 fl, mean corpuscular haemoglobin 32.4 pg, white blood cell count 19.6×10^9/l with left shift but

Aetiologies of DIC[8]

Obstetric complications
- abruptio placentae
- septic abortion and chorioamnionitis
- amniotic fluid embolism
- intrauterine foetal death
- miscellaneous (degenerating hydatiform moles and leiomyomas, postpartum haemolytic–uraemic syndrome, abdominal pregnancy, tetracycline-induced hepatorenal failure, foetomaternal blood passage, saline- and urea-induced abortions)

Infections
- viral: herpes, rubella, smallpox, acute hepatitis, Reye's syndrome, cytomegalic inclusion disease, various epidemic haemorrhagic fevers, etc
- rickettsial: Rocky Mountain spotted fever, etc
- bacterial: meningococcal, septicaemia, particularly Gram-negative organisms
- mycotic: histoplasmosis, aspergillosis
- protozoal: malaria, kala-azar, trypanosomiasis

Neoplasms
- carcinomas: prostate, pancreas, breast, lung, ovary
- miscellaneous: metastatic carcinoid, rhabdomyosarcoma, neuroblastoma

Disorders of the haematopoietic system
- acute leukaemia: promyelocytic, etc
- intravascular haemolysis: transfusion of incompatible blood, drug-induced, paroxysmal nocturnal haemoglobinuria, sickle cell anaemia, fresh-water submersion
- histiocytic medullary reticulosis

Vascular disorders
- malformations: giant haemangiomas, aneurysms, coarctation of the aorta, Takayasu's aortitis, large prosthetic arterial grafts, cyanotic congenital cardiac lesions
- collagen–vascular disorders
- hypoxia and hypoperfusion

Massive tissue injury
- large traumatic injuries and burns

Miscellaneous
- acute iron toxicity, head trauma, snake-bite, anaphylaxis, concentration of vitamin-K-dependent coagulation factors, heat stroke, allograft rejection, graft versus host disease, severe respiratory distress syndrome, diabetic acidosis, status epilepticus, acute pancreatitis, homozygous deficiency of protein C

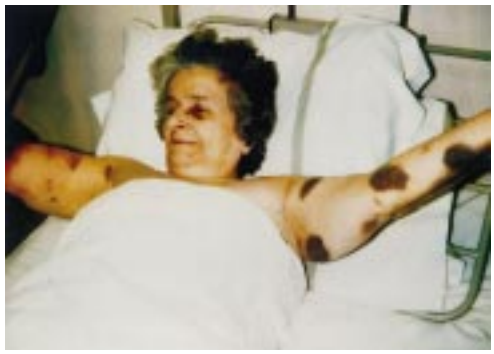

Figure The patient (reproduced with her permission)

City General Hospital, Newcastle Road, Stoke on Trent, Staffordshire ST4 6QG, UK
R K Kedia
A J Wright

Accepted 14 January 1999

Learning points

- quinine can cause thrombocytopenia and DIC
- any patient with DIC who is taking quinine should be checked for quinine-dependent platelet antibodies and quinine should be stopped
- such patients should be advised never to take quinine in any form including bitter soft drinks

no toxic granulation, and platelets 1×10^9/l. Prothrombin time was 22.1 s (normal range 13.9–17.9 s), partial thromboplastin time 24 s (18–22 s), fibrinogen 1.0 g/l (2–4 g/l), D-dimer >64 000 ng/ml (<500 ng/ml). Renal function was normal, albumin 26 g/l, bilirubin 19 mmol/l (1–17 mmol/l). Alkaline phosphatase and alanine transaminase levels were normal. ECG and chest radiography were normal.

A diagnosis of DIC due to septicaemia from a urinary tract source was made. She improved after six packs of platelets, two units of fresh frozen plasma, and intravenous cefuroxime 750 mg tid. Blood and urine cultures were subsequently shown to be negative. Further investigation showed negative antinuclear and rheumatoid factor, lupus anticoagulant, antistreptolysin titre and serological screening for common viruses. Platelet-associated immunoglobulin was 4.4 g/l (<1.6 g/l) with positive immunofluorescence with the addition of quinine sulphate at a concentration of 1 g/l.

On discharge one week later she had recovered fully with all abnormal investigations within the normal range. She was advised to avoid all quinine-containing substances.

Discussion

Our patient had DIC with positive quinine-mediated platelet antibodies for which the only demonstrable cause was exposure to therapeutic doses of quinine sulphate. Only five other patients with DIC secondary to quinine sulphate have been reported in the medical literature.[1–3] Our patient developed DIC after only two doses of quinine sulphate separated by a time interval of 3 months, raising the possibility of sensitisation.

Connellan *et al*[4] suggested that quinine induces widespread conformational changes in platelet membrane antigen which exposes neoantigens and may induce quinine-associated antibodies. These antibodies, in the presence of quinine, may bind a range of platelet glycoproteins by the Fab domain rather than the Fc, suggesting that platelet destruction is not complement mediated.[5] Previous studies of quinine-dependent platelet antibodies on platelets from patients with Bernard-Souleir or Glanzmann's disease showed heterogenic populations of antibodies with different specificities within individuals now shown to be GPIb, GPIIb, GPIIIa and GPIx. Chong *et al*[6] have used monoclonal antibodies to show that the predominant drug-dependent antibodies in quinine-induced thrombocytopenia react with the membrane-associated GPIb/IX complex; some of their patients showed antibody binding to GPIIIa but the concentration of this antibody was considerably less than that of the corresponding antibody to GPIb/IX. GPIIIa is present on the surface of endothelial cells[7] and a possible explanation of the mechanism of quinine-dependent activation of coagulation and subsequent DIC in our patient is via antibody interaction with GPIIIa from endothelial cells, with subsequent release of procoagulant material from these cells.

DIC is a rare but recognised complication of quinine sulphate which may be fatal.[3] We recommend that any patient on quinine who presents with DIC should be checked for quinine-dependent platelet antibodies and quinine should be discontinued forthwith.

We thank Dr M Spiteri and Dr A Sullivan for their valuable suggestions and Miss N Mali who prepared the typescript.

Keywords: quinine; thrombocytopenia; adverse drug reaction; disseminated intravascular coagulation

1 Elliot HL, Trash DB. Intravascular coagulation induced by quinine. *Scot Med J* 1979;**24**:244–5.
2 Barr E, Douglas JF, Hill CM. Recurrent acute hypersensitivity to quinine. *BMJ* 1990;**301**:323.
3 Spearing LR, Hickton CM, Sizeland P, Hannah A, Bailey RR. Quinine-induced disseminated intravascular coagulation. *Lancet* 1990;**336**:1535–7.
4 Connellan JM, Deacon S, Thurlow PJ, Dauer R. Changes in platelet function and reactivity induced by quinine in relation to drug induced immune thrombocytopenia. *Thromb Haemost* 1989;**62**:46 (abstr 105).
5 Christie DJ, MullIn PC, Aster RH. Fab mediated binding of drug dependent antibodies to platelets in quinine and quinine-induced thrombocytopenia. *J Clin Invest* 1985;**75**: 310–4.
6 Chong BH, Horne S, Berndt MC, Chesterman CN. Studies of the interaction of the quinine/quinidine-dependent antibodes with platelet glycoproteins Ib-IX and IIB/IIIA. *Thromb Haemost* 1989;**62**:46 (abstr 106).
7 Knappe W, Dorken B, Grieks W, *et al*, eds. *Leucocyte typing IV - white cell differentiation antigen.* Oxford: Oxford University Press, 1989; pp 965–6.
8 Grosset ABM, Rodgers GM. Acquired coagulation disorders. In: Lee GH, Foerester J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, eds. *Wintrobe's clinical hematology*, 10th edn. Baltimore: Williams and Wilkins, 1997; pp 1740.