Teaching Point
(Section Editor: K. Kühn)

Supported by an educational grant from Fresenius Medical Care

The lady who had muscle cramps and developed thrombotic microangiopathy

Gary Rabetoy, Matthew Hansen, Godela Brosnahan and Leah Hartung

Introduction

Quinine induced haemolytic uraemic syndrome is a well described clinical entity consisting of microangiopathic haemolytic anaemia, thrombocytopenia, and acute renal injury that occurs following exposure to quinine in any of its forms. Patients will usually present with a history of fever, chills, nausea, vomiting, abdominal pain, diarrhoea and oliguria that begins within hours following quinine ingestion. Serologic evaluation, when done, has demonstrated antibodies against any or all of the haematopoietic cell lines including platelets, erythrocytes and granulocytes. Treatment has included supportive care, haemodialysis, steroids, cytotoxic medication, plasmapheresis, and splenectomy. Plasmapheresis has been very effective in most of the patients studied but has not always resulted in complete recovery. In this ‘Teaching Point’ two cases of HUS are described with documentation of quinine dependent antibodies.

Case report

A 50-year-old female was admitted to another hospital on April 4, 1992, because of 2 days of nausea, vomiting, abdominal and bilateral flank pain, as well as headaches and decreased urine output. Prior to this admission she had been well. Her past medical history was remarkable for long-standing essential hypertension and recurrent uncomplicated urinary tract infections. Medications at the time of admission included clonidine 0.3 mg three times a day, and for the week prior to admission amoxicillin and ibuprofen after a tooth extraction.

The evening before admission she took one tablet of 260 mg quinine for leg cramps. She was a married homemaker with seven children and no exposure to tobacco or alcohol use. Family history was positive for diabetes with kidney problems. Initially she was thought to have viral gastroenteritis. However, during the following 48 h she developed oliguric renal failure with an increase in serum creatinine from 1.5 to 5.9 mg/dl, microscopic haematuria, a decrease in platelet count from 179 000 to 60 000/mm³, and a decrease in haematocrit from 43 to 33%. Serum LDH was 5166 U/l. Because of worsening renal failure she was transferred to University Hospital.

On arrival, physical exam disclosed a pulse rate of 72 beats/min (BPM), blood pressure 176/106 mmHg, temperature 36.7°C, and a respiratory rate of 20 breaths/min. Physical examination was remarkable for bilateral costovertebral angle tenderness and bilateral lower extremity oedema. Laboratory studies revealed a serum creatinine of 5.9 mg/dl, a BUN of 56 mg/dl, LDH of 4734 U/l, with an AST of 762 U/l, a serum bilirubin of 1 mg/dl, white blood cell count 8300/mm³, a haematocrit of 33%, and a platelet count of 47 000/mm³. A urinalysis showed multiple dysmorphic red cells with red blood cell and granular casts. Further workup showed a normal renal ultrasound, negative anti-nuclear antibody, and anti glomerular basement membrane antibodies, normal C3 and C4, with negative serologies for hepatitis A, B, and C, and negative urine culture. A blood smear showed signs of active haemolysis with schistocytes, a white cell left shift, and a decrease of platelets. A diagnosis of idiopathic haemolytic uraemic syndrome was made. The patient was treated with plasmapheresis for seven consecutive days, then every other day for a total of eleven treatments with fresh frozen plasma as the replacement fluid. She also received high dose solumedrol 500 mg intravenously for three consecutive days, then oral prednisone 100 mg/day. She required seven red blood cell transfusions and haemodialysis throughout her hospital stay. Her platelets gradually increased to 400 000/mm³, her haematocrit stabilized, and her LDH returned to normal. After hospital discharge she slowly regained

Correspondence and offprint requests to: Dr Gary Rabetoy, University of Utah, Division of Nephrology, 50 North Medical Drive, Front Dumke Building, #535 Salt Lake City, UT 84112, USA.

© 2000 European Renal Association–European Dialysis and Transplant Association
sufficient renal function for dialysis to be stopped and her serum creatinine stabilized at a new baseline of 2.5 mg/dl.

Further medical course was uneventful until July 20, 1995 when she had leg cramps and took a single tablet of 260 mg quinine. Thirty minutes later she developed nausea, blurred vision, headaches, diffuse myalgias (particularly in her lower back and paraspinal muscles), and chills. Once again, she presented to another hospital with a blood pressure of 210/130 mmHg and a fever of 38.8°C. Her haematocrit was 37% with a white blood cell count of 600/mm³ and a platelet count of 174 000/mm³. A blood smear revealed schistocytes. Urinalysis revealed microscopic haematuria. After admission her white blood cell count rose spontaneously to 7800/mm³ with a left shift within 12 h of admission. The LDH was 2219 U/l on July 21, 1995. Initial treatment with intravenous methylprednisolone was commenced, but over the next 3 days she developed oliguric renal failure with a rise in creatinine to 9.5 mg/dl, a fall in haematocrit to 28% and a platelet count decrease to 40 000/mm³. On July 24, 1995, she was transferred to University Hospital for dialysis. On arrival she was afebrile with a pulse of 76 BPM, a blood pressure of 180/110 mmHg, and a respiratory rate of 16 breaths/min. She had purpura over her arms and trunk with petechiae on her left cheek. Both lower extremities had pitting oedema to the knees, but the rest of her physical examination was unremarkable. Laboratory studies at this time revealed a haematocrit of 29%, white blood cell count of 11 000/mm³, platelets 87 000/mm³, with serum LDH of 923 U/l, and serum creatinine of 9.8 mg/dl. Prothrombin time and partial thromboplastin time were normal, a haptoglobin was 23 mg/dl, but her blood smear at this time showed no signs of active haemolysis. A diagnosis of quinine induced haemolytic uraemic syndrome with partial recovery was made. The patient was conservatively treated with dialysis, and plasmapheresis was not performed because the platelet count and LDH had already improved. Within 7 days she had a normal platelet count, as well as LDH with a stable haematocrit, but still required haemodialysis. She was discharged with the recommendation to strictly avoid future quinine ingestion, including quinine-containing beverages. One month later she had regained sufficient renal function for dialysis to be stopped, and over the next few months her creatinine returned to her baseline level of 2.6 mg/dl. On May 14, 1997 she returned to the nephrology clinic where blood was drawn to determine whether her serum contained quinine dependent platelet antibodies. Normal subjects and a patient with known quinine-dependent platelet antibodies served as negative and positive controls. The results are shown in Figure 1. This patient had significantly elevated quinine dependent IgG antibodies almost 2 years after her last episode of quinine induced haemolytic uraemic syndrome.

Discussion

Since 1865 it has been known that quinine is capable of producing thrombocytopenia in susceptible individuals [1]. Some 114 years later the coincidence of disseminated intravascular coagulation, renal failure, and quinine ingestion was reported [2].

An overview of previously reported cases of haemolysis and quinine induced renal insufficiency has been recently published [3]. Certain individuals may have recurrent episodes of thrombocytopenia [1] and disseminated intravascular coagulation [4] without [1,4] and with [4,5] renal insufficiency, which on occasion may occur over a time span of some 22 years [5].

Although most of the cases have been attributed to haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura (thrombotic microangiopathy), only three cases have had biopsy evidence of this entity [3,5,6]. In other cases, however, the renal failure was found to be due to acute interstitial nephritis [7,8]. Clearly then, there is a broad spectrum of disease that can be associated with quinine. Milder cases likely go
unrecognized by the medical community, often being attributed to a flu-like illness by the patient and perhaps even by the physician. In fact we saw a second case involving a 77-year-old female with a similar picture involving the ingestion of quinine who had a rather similar course. Quinine-dependent antibodies (Figure 2) were also demonstrated in this case. She recovered with treatment that included haemodialysis, plasmapheresis using fresh frozen plasma and cryosupernatant replacement fluid and was counselled to forevermore avoid quinine.

Why some individuals are more susceptible than others is not clear. However, numerous studies have attempted to define the pathogenesis of this entity. The bulk of attention has been focused on the role of antibodies [4,9,10–15]. Red cells, white cells and platelets may all be involved. In a human umbilical vein endothelial cell (HUVEC) system, quinine-dependent antibody binding has been demonstrated [12]. Similarly, augmentation of neutrophil adhesion to HUVEC by quinine has been shown in the absence of quinine-dependent antibodies to HUVEC [11]. Where platelets are concerned, most of the quinine-dependent antibodies recognize the GPIIB/IIIA and GPIB/IX glycoprotein complexes [10]. The GPIIIA receptor exists on endothelial cells also [4], offering a possible explanation for at least one mechanism of action.

Interestingly, quinine dependent antibodies may be consumed early in the course of the illness [4] resulting in low or theoretically undetectable levels initially. Retrospective analysis, however, indicates that once the quinine dependent antibody is formed, it may remain at a high level for many months to years (Ref. [4] and present case 1).

Although not definitively proven, it has been proposed that following drug administration, in vitro metabolism occurs followed by blood cell interaction. This leads to the generation of loose or stable cell drug complexes and the creation of neoantigens, an immune response and antibody production that may be drug dependent (as in the case of quinine) or autoantibody in nature. Cell destruction can be the final result. This immune response appears to be unpredictable. It is thought that the primary immune response takes at least 6 days to develop. However, once this has taken place, even months or years later, a single dose of the offending agent, regardless of its size, may trigger an immediate response. We (and others also) have amply demonstrated this in the case of quinine. With rare exception, genetic factors or a history of allergy do not appear to be associated, though in general where sex was noted (including one case of interstitial nephritis), female adults seem to be more often affected [14]. Indeed, in the quinine cases reported [2,3] and present cases, 21 of 25 cases were female.

In summary the following points are worth noting. A broad spectrum of disease manifestations may be present where quinine is concerned. Owing to the widespread, often inconspicuous exposures and the non-specific nature of symptoms and signs that may occur, an exceedingly high level of suspicion on the part of the clinician must be maintained. It would appear that the susceptible patient, once having developed these apparently long lasting antibodies remains at risk indefinitely. As there is no animal model, dose response relationships in the induction of quinine sensitivity remain unknown [16]. Although most reported cases have been associated with the ingestion of quinine tablets, recurrent renal failure has been precipitated by the generally smaller amounts of quinine present in tonic/mineral water [5]. Simply warning the patient may not be sufficient to prevent recurrence [13]. As there are no randomized control trials and some diagnostic imprecision, the best treatment regimen remains uncertain. Most success has been with plasma exchange/replacement often in combination with steroid administration; although patients may spontaneously and/or with supportive care recover.
as well [13]. A recently published algorithm, however, appears to support only discontinuation of the offending agent, where drug induced haemolytic uraemic syndrome is felt to be present [17]. As the true extent of the problem is unknown, we strongly concur with the recommendation that a public study be conducted [16]. At the very least, prescription and non medicinal labelling should indicate the symptoms, signs, and types of quinine toxicity (as exemplified in our and others’ patients) that may occur so that public awareness may be heightened, and prompt medical attention sought as necessary. Elimination of quinine availability would be another option.

**Teaching point**

(i) As quinine may cause a wide variety of clinical manifestations, always perform a thorough history of possible exposures.
(ii) Although not foolproof, failure to make the correct diagnosis the first time may well result in a serious (and expensive) yet preventable recurrence.

**References**