ACUTE RENAL FAILURE FOLLOWING QUININE POISONING*

MORRIS NOTELOVITZ, M.B., B.CH., M.D. (RAND), M.R.C.O.G., Head of the Department of Obstetrics and Gynaecology, DESMOND DALRYMPLE, M.B., B.CH. (RAND), Registrar, Department of Obstetrics and Gynaecology, AND MALCOLM FUNSTON, M.B., B.CH. (RAND), Registrar, Renal Unit, Addington Hospital, Durban

Acute renal failure during or subsequent to pregnancy is usually due to an ischaemic tubular necrosis following shock precipitated by haemorrhage, sepsis or intravascular haemolysis. Quinine sulphate, when used as an abortifacient early in pregnancy, is a less commonly recorded but frequently fatal aetiological agent. A patient exhibiting acute renal failure following the ingestion of quinine sulphate during the eighth week of her pregnancy presented recently to the Gynaecological Unit at Addington Hospital, Durban. Complete recovery occurred following haemodialysis and intensive medical management.

Case Report

A 21-year-old married White female (of Spanish descent) was referred to Addington Hospital from an outlying town, with the following history. Five days before admission, the patient had ingested 9 quinine tablets (gr. 90) in order to procure the abortion of an 8-week pregnancy. This was followed by a self-administered salt-and-water douche. Approximately 24 hours later she experienced some lower abdominal pain, followed by vaginal bleeding and the passage of a few small blood clots. She then noticed that her eyes had become deeply jaundiced and that she was passing small and less frequent amounts

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of a very darkly coloured urine. She consulted her general practitioner who immediately referred her to our unit. On admission, her general condition was satisfactory. Her blood pressure was 130/90 mmHg with a pulse rate of 112/minute. Both the volume of the pulse and the nail-bed capillary-filling time were normal. She was mildly pyrexial (99°F). The most obvious abnormal features were her markedly jaundiced conjunctivae. Small subconjunctival haemorrhages were noticed in her right eye, but both pupils were normal in size and reacted equally to light. Mentally, she was drowsy but responded to the spoken word. There were no localizing signs. The cardiovascular and respiratory systems were normal. Although the abdomen was tender, there was no evidence of peritonitis. Normal bowel sounds were present. Neither the liver nor the spleen was enlarged.

Speculum examination revealed non-offensive dark blood issuing through the cervical os. No evidence of trauma to the cervix could be detected. The cervix on bimanual examination was found to be 1-finger dilated. The uterus was bulky and was erect, mobile and nontender. Apart from some bilateral tenderness, the adnexae were clear.

On catheterization of the bladder with an indwelling catheter, only 40 ml of dark red urine was obtained which gave a strong positive reaction to occult blood +++ and albumin ++++. A subsequent report from the Government Laboratories confirmed the presence of quinine in the urine. Unfortunately a quantitative assessment was not given.

Examination of the blood disclosed that the serum was pink. The initial haemoglobin level was 11.9 g/100 ml, with a haematocrit value of 31%. The white cell count was 40,000 cells/mm³; platelets 43,000/mm³; methaemoglobin was present in the serum. The blood film showed anisocytosis, polychromasia, microspherocytes ++, Burr cells ++; neutrophils showed a shift to the left. The haematologist commented that morphological evidence of haemolytic anaemia was present. The blood urea was 160 mg/100 ml; sodium 131 mEq./litre; potassium 4.8 mEq./litre; chloride 103 mEq./litre; bilirubin 11 mg/100 ml. Blood gas studies revealed the following: blood pH 7.38; blood PCO₂ 28 mmHg; blood base deficit 12 mEq./litre; standard plasma HCO₃ 14 mEq./litre; blood PO₂ 140 mmHg; blood O₂ saturation 99%. The direct Coombs test was negative. There was no growth on aerobic and anaerobic culture of the blood and a high vaginal swab. The electrocardiogram was essentially normal.

A central venous monitor was erected via the external jugular vein and gave a reading of 4 cm of water. The base deficit was corrected with an 8.5% sodium bicarbonate solution and 2 units of Plasmalyte B transfused to correct the hypovolaemic state. When this did not produce a diuresis, a provocative dose of 100 mg furosemide (Lasix) was administered intravenously, but this produced only 40 ml of urine over a period of 4 hours. The patient was then placed on a renal failure regimen and given an antibiotic cover of cephaloridine and ampicillin.

During the next 12 hours her condition deteriorated in that she became semicomatose and began to vomit more copiously. This necessitated intermittent nasogastric suction through a Ryle's tube. She remained afebrile, however, while her pulse rate settled to 100/min and her blood pressure remained constant at about 120/60 mmHg. The haemoglobin fell to 9.9 g/100 ml and the total bilirubin to 6 mg/100 ml, but her blood urea rose to 208 mg/100 ml. The electrolytes still remained within normal levels. She was transfused with 2 units of fresh blood, and an evacuation of the uterus was performed under local anaesthesia. Degenerate products of conception were removed. Despite the correction of her anaemia, and negative fluid balance, the urinary output since admission was only 200 ml. Approximately 24 hours after admission, the patient had an epileptiform convulsion. It was then decided to initiate renal haemodialysis.

During the following 8 days, the patient was dialysed on four occasions. Her clinical condition improved daily, but it was not until the 11th day following admission that a diuresis was established (Fig. 1). Thereafter the urinary output and concentrating ability of the kidney improved daily, reaching a maximum diuresis of 4 litres on the 22nd day and an osmolality of 355 milliosmols/kg on the 25th day. As expected, the blood urea remained elevated for much longer, but on the day of discharge it had settled to 46 mg/100 ml. Creatinine clearance tests performed on the 29th and 36th days respectively showed values of 25 and 47 ml/min. (A repeat creatinine clearance 2 months after discharge was normal.) The electrolytes remained normal throughout her entire period of hospitalization, while the haemoglobin level became stabilized at between 9 and 10 g/100 ml. The platelet count recovered spontaneously (Fig. 2). Since the patient came from a Mediterranean area the possibility of her having a glucose-6-phosphate dehydrogenase deficiency (which predisposes to the haemolysis of red blood cells by antimalarial drugs) was excluded shortly after admission. Repeated liver-function tests showed no evidence of hepatic involvement. A biopsy specimen of the kidney could not be obtained.

Apart from a non-specific generalized skin-rash which developed subsequent to her dialysis, the patient made a relatively uneventful recovery. Remaining afebrile and symptom-free, she was eventually discharged fit and well, 37 days after admission.

**DISCUSSION**

Although the patient reported above had positive evidence of pelvic sepsis, the mildness of the infection and the absence of signs of endotoxic or hypovolaemic shock excluded these factors as being the precipitating cause of the acute renal failure.

Apart from the acknowledged ingestion of quinine and its demonstration in the urine, she exhibited a number of the known side-effects of quinine toxicity, namely, sensitivity reactions affecting the red cells, platelets and probably the skin, and direct toxic reactions which affected her gastro-intestinal and central nervous systems. The relationship of quinine sulphate ingestion 3 days before the onset of the oliguria and haematuria suggests that this agent was responsible for haemolysis followed by tubular necrosis and subsequent acute renal failure.

The 'sensitivity' side-effect of acute haemolytic anaemia due to quinine is most often seen during early pregnancy, and there are few instances where acute renal failure,
Quinine is not commonly used today, its main indication probably being its use in resistant falciparum malarial infections. Although abortion has followed toxic doses, this is usually a manifestation of a general toxic effect, rather than a direct uterine action. Repeated clinical trials have shown that an oxytocic effect is only present in established labour and that it is ineffective in inducing premature labour.\cite{56} However, among lay persons, quinine has the reputation of being an abortifacient, and this, together with a complete lack over the control of its sale, constitutes the major danger of its use. In addition, there

Fig. 1. Clinical course of patient.

Fig. 2. Blood picture changes of patient.
is a wide variation in the tolerance to quinine—as little as 0.4 g proved fatal in one instance, although the fatal dose for adults is usually given as 8 g. Symptoms are likely to occur in anyone taking a single dose larger than 5 g (gr. 60).13 The amount consumed by our patient was approximately 6 g (gr. 90).

The mechanism whereby quinine induces a haemolytic reaction is not known, but Freedman and associates postulate that it operates through one of 3 pathways: a direct haemolytic action on the erythrocyte; production of a 'hypersensitivity' reaction resulting in an 'immuno-

haemolytic' anaemia; or by a direct action in genetically susceptible individuals who have an erythrocyte deficiency of glucose-6-phosphate dehydrogenase. The intravascular haemolysis thus produced leads to an ischaemic tubular necrosis caused by renal vascular spasm, rather than by a direct effect of the precipitated haemoglobin or cellular casts in the kidney.

In instances of acute drug poisoning early treatment not only is life-saving, but also appreciably shortens the period of morbidity. This is particularly true of quinine, since it is virtually completely absorbed from the upper gastro-intestinal tract, with peak plasma concentrations appearing within 1-3 hours after ingestion.14 It appears unaltered in the urine within the first ½-hour,15 the major excretion occurring via the kidneys. Excretion of a single dose will be nearly complete in 24 hours.16 Therefore gastric lavage, if used soon after ingestion, may be effective in preventing absorption, while acidification of the urine is said to produce maximal excretion. An increased excretion will also result by promoting an increased renal flow by the use of osmotic diuretics, such as mannitol and intravenous fluid therapy.17,18

Quinine sulphate is dialysable and dialysis may therefore be used in the early treatment of quinine overdosage, and not only in cases complicated by acute renal failure. Whereas Markham et al.19 and others advocate the use of peritoneal dialysis as an adjunctive aid in the presence of a potentially lethal dose of quinine, Donaidio et al.20 have reported more recently that the removal rate of quinine by peritoneal dialysis is trivial. The poor peritoneal clearance of quinine is thought to be due to plasma protein binding—70% of quinine in the plasma is bound.1 The preliminary studies have shown that haemodialysis with a twin-coil Kolff kidney is a much more effective method than peritoneal dialysis to remove the toxic metabolites—should be considered.

Unfortunately, because of individual variations in response to quinine (see above) one cannot determine at what particular dose level haemodialysis should be considered. Thus, Hillman and Harpur21 and Taggart et al.22 report instances of toxic symptoms occurring at comparatively low serum levels. It has been suggested that the final decisions should be governed by considering repeated serum levels of quinine, together with the severity and the rate of progress of the symptoms. Oliguria, as in the case reported above, is a mandatory indication for dialysis.

Treatment for acute quinine poisoning should commence with a gastric lavage. In patients with intact renal function, an increased excretion of the quinine will be obtained by acidification of the urine and the promotion of a brisk diuresis with mannitol and intravenous fluids.

Where symptoms are severe, the serum levels remain elevated or oliguria is present, haemodialysis (or less effectively, peritoneal dialysis) is indicated. In the absence of either of the last two methods, a 20-pint exchange transfusion—to remove the toxic metabolites—should be considered.

It has been shown that recovery from ischaemic tubular necrosis can be expected if the patient survives long enough (3-30 days) to allow for regeneration of the damaged tubular lining cells and basement membrane. Although a confirmatory histological diagnosis was not obtained, our case represents a complete recovery from acute renal failure subsequent to quinine poisoning.

**SUMMARY**

Acute renal failure developed in a 21-year-old woman following the ingestion of quinine sulphate in an attempt to induce abortion. Complete recovery occurred following early haemodialysis and intensive medical care. Susceptibility to the toxic effects of quinine in early pregnancy occurs at varying dosages and may affect other target organs, producing, for instance, deafness and blindness. Early treatment by gastric lavage, acidification of the urine, osmotic diuretics and intravenous fluids will frequently result in a reversal of toxic symptoms. Failure to improve and/or oliguria are mandatory indications for haemodialysis.

A brief review of the literature regarding the toxic effects of quinine sulphate when used as an abortifacient is presented.

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**REFERENCES**