case against aluminium as not proved. But patients who dialyse in areas where the aluminium or manganese content of water is high should be supplied with deionisers. A water softener is inadequate.

We thank the water authorities of our region for supplying us with the results of their analyses, and Mr Bob Dixon for advice on the statistical analyses.

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Fulminant Wilson's disease with haemolysis and renal failure: copper studies and assessment of dialysis regimens

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Summary

Two girls, aged 12 and 17 years, presented with hepatocellular dysfunction and severe haemolysis due to Wilson's disease (hepatolenticular degeneration). This was accompanied by acute renal failure. In the absence of renal function sufficient for the urinary excretion of penicillamine, studies were performed to assess the potential of peritoneal dialysis, ascites removal by ultrafiltration-reinfusion, and haemodialysis as alternative excretory pathways for copper. The greatest amount of copper, as judged by rising bath concentrations, seemed to be eliminated with haemodialysis. But this was accompanied by a progressive increase in serum copper concentrations with rapid clinical and biochemical deterioration leading to death within 48 hours. A small amount of copper was lost with ascites removal. Significant amounts of copper were removed during peritoneal dialysis (36 μmol/day (2287 μg/day)), although a clinical response was not evident before haemodialysis was introduced. The administration of penicillamine orally, intravenously, or intraperitoneally produced no measurable increase in copper excretion into the peritoneal dialysate.

Hence peritoneal dialysis alone appears to offer the greatest potential benefit with regard to both eliminating copper and altering the course of this fulminant form of Wilson's disease.

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Introduction

Wilson's disease (hepatolenticular degeneration) usually presents with clinical signs of chronic hepatic or neurological dysfunction. Haemolytic anaemia may precede these manifestations[1] and is usually brief. Rarely, however, when haemolysis occurs together with hepatic decompensation, rapid deterioration ensues if the condition is not diagnosed early.[2] We describe here two fatal cases of Wilson's disease. Both patients developed hepatic failure, severe haemolysis, and acute renal failure. Acute renal failure does not seem to have been reported before in association with Wilson's disease. Since the most effective chelating agent, penicillamine, is cleared from the plasma by the kidneys, peritoneal dialysis and haemodialysis were assessed in these patients as alternative means of eliminating the increased tissue copper stores. In addition, the role of penicillamine in the presence of renal insufficiency was evaluated in relation to peritoneal dialysis.

Case 1

This premenarchial 12-year-old girl experienced malaise with irritability and drowsiness 10 days before admission. Three days later profound anorexia developed with the passage of dark urine. She was feverish and had raised serum aspartate aminotransferase (SGOT) concentrations.

Over the next three days jaundice appeared, her level of consciousness deteriorated, and she was admitted to the Royal Victoria Infirmary.

Examination showed scratch marks, chest acne, and red striae on breasts, abdomen, and thighs. Ascites was present but not hepatosplenomegaly. Melaena stools were being passed and she was anuric. The diagnosis of Wilson's disease was suggested by the presence of Kayser-Fleischer rings.

Investigations confirmed haemolytic anaemia with haemoglobin concentration of 8·7 g/dl, reticulocyte count of 34%, and reduced plasma haptoglobins. The Coombs test gave a negative result. The blood urea concentration was 13·2 mmol/l (79·5 mg/100 ml) (normal < 7·0 mmol/l (42 mg/100 ml)). Prothrombin time was 36 s (control 13 s). Serum total bilirubin concentration was 1080 μmol/l (63·2 mg/100 ml) (normal < 17 μmol/l (0·99 mg/100 ml)), of which 800

μmol/l (46·8 mg/100 ml) was conjugated; serum alkaline phosphatase concentration was 23 IU/l (normal 20-90 IU/l), serum SGOT 190 IU/l (4-20 IU/l), and serum albumin concentration 22 g/l, with a total serum protein of 44 g/l. Smooth muscle antibody and hepatitis B surface antigen (HBsAg) tests were negative.

Treatment was started with oral neomycin, dextrose 10%, vitamin K_1, and fresh frozen plasma intravenously. Magnesium sulphate enemas were given and a low-salt magnesium trisilicate mixture instilled every two hours via a nasogastric tube together with penicillamine (240 mg). Ascitic fluid was removed by an ultrafiltration-reinfusion technique[3] on the third day of admission. By this time, however, the patient was deeply unconscious, the blood urea concentration had risen to 25 mmol/l (151 mg/100 ml), and she was severely acidotic. Haemodialysis was started using an Ultraflo coil (Travenol Laboratories) and copper-free circuiting at a flow rate of 103 ml/min and continued for six-hour periods on each of two successive days. The blood urea and electrolyte concentrations returned towards normal but the serum SGOT rose to 2360 IU/l. Early in the morning of the fifth day of admission ventricular ectopic beats developed, followed by unresponsive cardiac asystole. Histological analysis of liver tissue obtained a few minutes after death confirmed the presence of cirrhosis with massive necrosis; the renal tubules showed evidence of necrosis with some regeneration.

Subsequent investigation of the family failed to show the presence of consanguinity. Two younger sisters were, however, later diagnosed as having heterozygous Wilson's disease.

Case 2

This 17-year-old girl had a five-month history of oligomenorrhoea and acne. Two months before admission an influenza-like illness developed, accompanied by ankle swelling. Ten days after the development of jaundice she was admitted to the Royal Free Hospital with a diagnosis of liver failure.

On examination she was drowsy with a flapping tremor, deep jaundice, and an acneiform rash on her back and chest. She was passing only small amounts of black urine. There was bruising on the limbs, and ascites and peripheral oedema were present. There was palpable hepatosplenomegaly. Slit-lamp examination confirmed the presence of Kayser-Fleischer rings and the diagnosis of Wilson's disease. Investigation showed haemolytic anaemia, with a haemoglobin of 8·3 g/dl, reticulocyte count of 26%, reduced plasma haptoglobins, and negative Coombs test result. The white cell count was 15×10^9/l with neutrophilia. The blood urea concentration was 16·5 mmol/l (99·4 mg/100 ml). Liver function values were abnormal: serum bilirubin concentration was 560 μmol/l (32·7 mg/100 ml) (420 μmol/l (24·6 mg/100 ml) conjugated), serum alkaline phosphatase concentration 4·0 King-Armstrong units 100 ml (normal 3-13), and serum SGOT 85 IU/l (normal 4–15). Serum albumin concentration was 22 g/l with total protein 55 g/l. Smooth muscle antibody was present at a titre of 1/10 and she was negative for HBsAg.

Examination of urine confirmed the presence of casts, red cells, and haemosiderin.

A liver failure regimen was started, similar to that described above. After six days the blood urea had risen to 47 mmol/l (283 mg/100 ml) and she became increasingly drowsy. Peritoneal dialysis was started and penicillamine administered according to the schedule described below. By the 19th day a severe metabolic alkalosis due to large gastric aspirate volumes supervened. At this time the serum SGOT had risen to 209 IU/l. Peritoneal dialysis was continued, and six days later haemodialysis was started because of the continued instability of her acid-base status. Severe haemorrhagic gastritis followed and she died two days later. Post-mortem liver histology showed cirrhosis with considerable necrosis and inflammatory change, and renal tissue showed tubular necrosis with regeneration.

Screening of the family disclosed a younger sister with presymptomatic Wilson's disease.

Methods

Fluid copper concentrations were measured by atomic absorption spectrophotometry and tissue levels were determined by neutron activation analysis. All samples were obtained by "copper-free" equipment and techniques. The diagnosis of Wilson's disease was confirmed in each case by the appropriate investigations (table I).

Case 1—In this patient the outcome of ascites removal was compared with that in three patients with alcoholic cirrhosis. The technique of ultrafiltration-reinfusion of ascitic fluid uses a polyacrylonitrile membrane and plastic disposable circuit (Rhodiascit, Rhône-Poulenc, France) claimed by its manufacturers to be copper-free. Clogging of the membranes, due to the high-protein concentration, allowed the extraction of only a limited amount of ascites ultrafiltrate in this patient. This was collected over 2·8 hours and an aliquot of the total analysed for copper. The procedure was repeated in the case of three patients with alcoholic cirrhosis; the mean time for collection of the ultrafiltrate was 9·6 hours. Serum copper was also measured daily. During two six-hour periods of haemodialysis arterial and venous line blood samples were taken together with bath water specimens, before and after dialysis sessions.

Case 2—In this patient studies were performed during peritoneal dialysis. The amount of copper excreted into the peritoneal dialysate was determined and compared with that of three control subjects with renal failure. The mean copper concentration of 12 samples of dialysis fluid (0·31 μmol/l (1·98 μg/100 ml)) was obtained by flushing through the administration set and bypassing the patient. The volume of each sample of dialysate obtained from the patient was about two litres. In the patient with Wilson's disease the mean concentration of 25 samples collected on different occasions and representing 50 litres of dialysate was 1·32 μmol/l (8·41 μg/100 ml). The net concentration of copper in the dialysate alone could therefore be derived.

TABLE I—*Copper studies in patients with Wilson's disease*

Investigations	Case 1	Case 2	Normal range
Serum copper (μmol/l)	33	45	11-25
Whole blood copper (μmol/l)	47	43	16-25
Urinary copper excretion (μmol/l)	Anuric	5·5*	1·1
on penicillamine 500 mg/day (μmol/day)	Anuric	12·2*	
Serum caeruloplasmin (mg/l)		250	270-380
Serum copper oxidase (Ravin units)	0·03	0·025	0·2-0·4
Liver copper (μmol/g dry weight)	8·59	6·94	0·14-0·74
Kidney copper (μmol/g dry weight)	16·05	2·51	0·88-0·55
Cerebral cortex copper (μmol/g dry weight)	2·05	3·65	0·21-0·61

*Mean urine volume 130 ml/day.
Conversion: SI to traditional units—Copper: 1 μmol/l ≈ 6·4 μg/100 ml; 1 μmol/g ≈ 64 μg/g.

Results

The results are shown in table II.

Ascites ultrafiltration-reinfusion in Wilson's disease achieved a copper excretion rate of 23 μmol/h (1461 μg/h) compared with 1·1 μmol/h (70 μg/h) in alcoholic cirrhosis. The total amount of copper removed from the patient with Wilson's disease was about six times that removed from the controls.

Haemodialysis produced a bath copper gain of 675 μmol (43 mg) over two days. This occurred over two six-hour sessions, so that the apparent net copper excretion by this route was 56 μmol/h (3558

TABLE II—*Effect of dialysis regimens on copper excretion*

	Patient		Controls
Ultrafiltration-reinfusion in case 1			
			(3 with alcoholic cirrhosis)
Mean ultrafiltrate volume (ml)	998		6249
Mean ultrafiltrate copper (μmol/l)	63·40		1·69
Meen net copper excretion (μmol)	63·2		10·5
Haemodialysis in case 1			
	1st session	2nd session	
Serum copper (μmol/l)			
Arterial	38	142	
Venous	42	153	
Bath copper (μmol/l)			
Before dialysis	2·0	1·3	
After dialysis	4·0	2·0	
Bath volume (l)	250	250	
Bath copper gain (μmol)	500	175	
Peritoneal dialysis in case 2			
			(3 with renal failure)
Mean volume of dialysate (ml)	2000		2000
No of dialysate samples	25		6
Mean net dialysate copper (μmol/l)	1·01		0·11
Mean daily copper excretion (μmol)*	36·40		3·96

*Calculated on basis of dialysis for 18-hour day at 2 l/h.

μg/h). On the other hand there was a progressive rise in serum copper concentration from 39 μmol/l (284 μg/100 ml) (before dialysis) to 86 μmol/l (548 μg/100 ml) (after dialysis) on the first day and from 139 to 150 μmol/l (885-955 μg/100 ml) on the second day of haemodialysis. This was reflected in the studies of arterial and venous line blood. There was an arteriovenous difference of 4-11 μmol/l (25-70 μg/100 ml), which, if a whole blood flow rate of 103 ml/min and a packed cell volume of 40% are assumed, corresponds to a release into the patient's circulation of 18 mmol (1143 mg) of copper over the two sessions.

Peritoneal dialysis resulted in a mean net dialysate copper of 1·01 μmol/l (6 μg/100 ml) in Wilson's disease and 0·11 μmol/l (0·7 μg/100 ml) in renal failure. Hence the excretion of copper across the peritoneum was enhanced tenfold in the patient with Wilson's disease. The dialysate flow rate was about 2 l/h, so this represented in absolute terms an excretion of 36 μmol/day (2287 μg/day). This amount compares favourably with that excreted in the urine of patients with Wilson's disease on penicillamine treatment but with normal renal function. In contrast with haemodialysis, serum copper concentrations remained fairly stable at 26 to 34 μmol/l (165 to 217 μg/100 ml) throughout the 18 days of peritoneal dialysis.

Since the peritoneum acts as a semi-permeable membrane, a study was performed in vitro to determine the influence of penicillamine on the diffusion of radiocopper across the dialysis membrane. The apparatus consisted of a two-piece glass system with two compartments[4] separated by a semipermeable membrane. A constant flow of a gas mixture (O_2 95% and CO_2 5%) ensured circulation of phosphate buffer and maintained the pH at 7·2. The ^{64}Cu-labelled samples were introduced into the larger compartment, after which aliquots were taken every 15 minutes from both compartments and the radioactivity measured. After counting for 100 seconds the samples were returned to their respective compartments in the system. Transfer of radiocopper across the membrane was expressed as the percentage of total activity transferred per unit time. With ^{64}Cu-cupric acetate in protein-free solution, a mean of 6% of the radioactivity was transferred in one hour (n = 3). The addition of human serum albumin (30 g/l) caused a dramatic fall in the diffusion rate (mean 0·3%, n = 3). When penicillamine was added to the ^{64}Cu-albumin solution in a final concentration of 0·1 mmol/l (n = 3) the transfer of ^{64}Cu rose to 8·1% at one hour, even greater than the diffusion rate of ^{64}Cu alone. These findings, in conjunction with the demonstration by Walshe[5] that the cupriuretic action of copper is probably due to its ability to free copper from its binding to plasma proteins and render it available for glomerular filtration, suggested that penicillamine should enhance the excretion of copper across the peritoneum.

In an attempt to confirm these observations in vivo, the effect of penicillamine on the excretion of copper into peritoneal dialysate was examined (in case 2). The drug was given orally in increasing doses of 250-750 mg and the response observed on repeated occasions. Next penicillamine hydrochloride was administered intravenously in 300-mg doses in 100 ml of saline (infused over 10-minute periods). Finally, 300 or 600 mg of penicillamine prepared in sterile solution was added to each litre of dialysis fluid, before peritoneal infusion. The peritoneal dialysate was collected for two hours before and eight hours after each test dose, and the copper concentration of each hourly collection measured. Regardless of the dose or route of administration, penicillamine did not increase the copper concentration of peritoneal dialysate.

Discussion

These two patients conform to the usual diagnostic criteria for Wilson's disease. In each case there were abnormalities of copper metabolism with high concentrations of tissue copper. Serum copper oxidase concentrations were also reduced, although in case 2 almost normal caeruloplasmin values were observed. This is occasionally seen in association with severe hepatic disease.[6 7]

Although haemolysis associated with hypercupraemia is now a well-recognised manifestation of Wilson's disease,[2 8-16] it is usually transient and self-limiting. Recently, however, a rapidly progressive course has been described in such cases.[17] Three girls, aged 8, 12, and 15, showed a three-stage clinical course. In the first four to six days there was fever and jaundice with raised serum transaminase (40-60 IU/l). In the next one or two days an acute intravascular haemolysis appeared. Finally, during the next week, hepatic failure developed. Cirrhosis and hepatic necrosis were found at necropsy, and, as in our patients, Kayser-Fleischer rings, hypercupraemia, and raised liver copper concentrations were evident.

Despite these similarities, it was the acute renal failure which dominated the clinical course in both of our patients. The latter was unusually rapid, meriting the epithet "fulminant." Such a course was presumably the outcome of several factors; haemolysis, hypotension, septicaemia, and hepatic failure were the most important. Extreme hypercupraemia may be crucial. The pathophysiology of the hypercupraemia and resulting haemolysis have been investigated.[16] Efflux of copper from hepatic storage sites, precipitated by intercurrent infection, seems possible, although the relevance of acute copper nephrotoxicity has yet to be shown.

Treatment of this type of patient must clearly include supportive treatment for hepatic and renal failure, as well as removal of copper. In the first patient haemodialysis produced an apparent net copper loss, but death followed two days later. This was preceded by a progressive rise in serum copper and both clinical and biochemical evidence of hepatocellular damage. Haemodialysis in the second patient also led to a rapid deterioration and death. The increase in serum copper, while being partly due to the mobilisation of copper stores, might well be related to the haemodialysis procedure. The use of a Watson-Marlow pump with a Silastic insert, as in this patient, can result in the release of haemoglobin from damaged red cells (up to 5 mg/l pumped).[18] The copper concentration difference of 4-11 μmol between the arterial and venous sides of the haemodialysis circuit suggests that haemolysis may have been enhanced in the presence of hypercupraemia, perhaps because of increased red cell fragility.

Another explanation for the rise observed is leaching of copper from the Ultraflo coil cuprophane membrane. One study[19] has shown that a mean rise in serum copper of 4·6 μmol/l (29 μg/100 ml) is seen after haemodialysis with this system. This is similar in magnitude to our observations, which included a striking rise in bath copper concentrations. None the less, the increase from 42 to 142 μmol/l (268-905 μg/100 ml) of serum copper between dialysis sessions suggests that another mechanism, perhaps secondary to large-scale redistribution of copper stores, was also responsible.

Ascites ultrafiltration-reinfusion in the first patient led to a significant loss of copper; for practical purposes, however, this could not be sustained. In the second case peritoneal dialysis for over two weeks produced a consistent net excretion of copper, comparable with the urinary loss in patients on chelation therapy. The serum copper concentration remained unchanged, but there was no significant clinical improvement. The contribution of penicillamine treatment was dubious in both cases, and, although in-vitro studies suggested that the drug would enhance excretion, this could not be shown in vivo by administering the drug by several routes. Such ineffectiveness would have been due to insufficient dosage or excessive binding of the drug to relatively fixed extravascular copper. Haemodialysis seems to be contraindicated, as consequent rapid mobilisation of copper corresponded to further clinical deterioration.

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Accidental percutaneous hexachlorophane intoxication in children*

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Summary

Eighteen children with normal skin were accidentally intoxicated by a talc powder containing 6% hexachlorophane. Four died and two remained paraplegic. The clinical picture was intracranial hypertension, eight patients developing signs of spinal cord damage. The condition seemed to result from massive intramyelinic oedema. In the spinal cord vascular disturbances may occur as mechanical complications of oedema, giving rise to permanent sequelae.

Introduction

Percutaneous hexachlorophane (HCP) absorption has caused severe and even fatal intoxication in patients with burns or ichthyosis.[1-4] HCP absorption through normal skin has been indicted as a cause of myelin lesions in premature infants bathed in 3% HCP solutions.[5-7] Fatal toxicity in full-term babies with normal skin has not been reported, nor have permanent neurological sequelae in man. Since myelin lesions due to HCP are usually reversible,[8 9] and the possible dangers from HCP remain a matter of controversy,[10] we report our experience of 18 children percutaneously intoxicated by a talc powder containing 6% HCP.

Patients and methods

The 18 children were admitted to this hospital between April and July 1972. The talc powder, which had been accidentally contaminated with 6% HCP, had been applied to the napkin area several times a day and allowed to remain between changes. HCP was sought in the serum in four cases and in the cerebrospinal fluid (CSF) in one.

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Four children died, in two of whom the brain and spinal cord were examined. Multiple sections of cortex, basal ganglia, cerebellum, brain stem, and spinal cord were embedded in paraffin and celloidin and examined by conventional techniques. Samples of white matter were taken from a frontal lobe fixed in formalin. After washing in 7% glucose phosphate buffer, small blocks were fixed in modified Karnovski fixative, postfixed in 2% phosphate-buffered osmium tetroxide, dehydrated, embedded in Araldite, and examined with a Siemens 101 electron microscope.

Results

The children (5 girls and 13 boys) were between 3 months and 3 years of age. Twelve were under 1 year. The onset of the disorder was marked by anorexia and vomiting, rapidly followed by agitation, drowsiness, and coma. Nine patients had a temperature of 38° C or more. Since the diagnosis was made retrospectively, the exact duration of use of the talc was unknown. The time between appearance of first symptoms and admission to hospital varied from a few hours to 15 days, though in 10 cases it was under 48 hours. Seventeen children had severe erythema in the napkin area resembling second-degree burns. Erythema preceded the neurological signs by three to 15 days in six cases and followed them in four. In the remaining cases either the erythema occurred simultaneously with the neurological signs or its time of appearance was unknown.

On admission 17 of the children had disturbances of consciousness. Fourteen had bilateral pyramidal tract signs and severe tremor, and 10 exhibited abnormal movements, with bouts of extensor hypertonia and pronation of the arms. Four patients had a history of "convulsions" before admission, though none was seen or recorded in the electroencephalogram during their stay in hospital.

Eight patients showed abnormal signs in the spinal cord. In two a full-blown picture of acute transverse myelitis at T8 and T4 was evident with normal consciousness in one. These two children remained paraplegic with sphincter dysfunction. Two infants had transitory paralysis of the legs followed within a few days by regressive spasticity. In the four children who died flaccid paraplegia was noted several hours before death.

Six patients had ocular abnormalities—namely, ocular jerks (four cases), mydriasis (one), and sixth-nerve palsy (one). In the infant with sixth-nerve palsy strabismus disappeared 27 days after admission to hospital, only to return in association with erythema of the buttocks, papilloedema, and blindness shortly after returning home, where the talc was again applied. Papilloedema was present in six cases, associated in at least three with other signs of increased intracranial pressure, such as suture diastasis and tense fontanelles. In one infant head circumference increased by 2 cm in four days.

Electroencephalography was performed at least once on 16 children. The tracings were abnormal in 15 cases, with bilateral slow waves predominantly during wakefulness and on awakening. In three cases