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Case Report

Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins

Bernhard Kreymann, Markus Seige, Ursula Schweigart, Klaus-Friedrich Kopp and Meinhard Classen

II. Department of Internal Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

Background: **Acute liver failure may be the first manifestation of Wilson disease. If copper elimination fails, liver transplantation is the only remaining therapeutic option. Albumin dialysis, a new method for the removal of protein-bound toxins, was performed in a patient with fulminant Wilson disease.**

Methods: **An 18-year-old man with Wilson disease presented with hyperacute liver failure, hepatic encephalopathy III°, oligo-anuric renal failure, haemolytic anaemia, rhabdomyolysis, pancreatitis and thrombocytopenia. He was treated with albumin dialysis using a 44 g/l albumin-containing dialysate and a slow dialysate flow rate (1–2 l/h). The other details of the technique used are similar to routine continuous veno-venous haemodiafiltration.**

Results: **One hundred and five milligrams of copper were removed by albumin dialysis within the first six treatments, resulting in normalisation of blood-copper levels. Successful treatment of the multiorgan failure was achieved. Hepatic encephalopathy improved within 2 days. The patient initially refused liver transplantation. Therefore 35 additional albumin dialysis treatments were performed. Forty-three grams of bilirubin (an indicator of detoxified substances in the liver) and 196 mg of copper were removed. Multiorgan failure, in particular hepatic encephalopathy, did not recur during 59 days of treatment. Eventually, the patient agreed to liver transplantation and that was successful.**

Conclusion: **Albumin dialysis is a new method for the effective treatment of fulminant Wilson disease, resulting in the removal of protein-bound toxins copper and bilirubin. It may serve as a new treatment option in hyperacute liver failure of other origin, acting as an extracorporeal detoxifier.**

Key words: **Albumin dialysis; Extracorporal liver assist device; Fulminant liver failure; Wilson disease.**

Wilson disease is a hereditary autosomal recessive disease of copper metabolism. The Wilson disease gene has been identified (1–3). In most cases, patients present either with chronic hepatic disease or with neurological manifestations (4,5). Rarely, hyperacute liver failure is the first manifestation of Wilson disease. The patients remain asymptomatic as long as copper can accumulate in the liver. However, when necrotic hepatocytes release high amounts of copper into the circulation, fulminant hepatic failure, haemolytic anaemia, and different degrees of acute renal failure occur (6–8).

If medical treatment fails, orthotopic liver transplantation is the only remaining treatment option, with a 90% survival rate after 1 year (9). Otherwise, nearly 100% mortality is to be expected in these patients (9). Only three patients are reported to have survived without transplantation, but these patients did not have renal failure (10–12).

To date, different methods have been explored for the replacement of the detoxification function of the liver, from routine methods like haemofiltration to highly sophisticated methods like bioreactor constructions (13). Recently, Stange et al. introduced a new detoxification method (referred to as MARS) for protein-bound substances in patients with liver failure and

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Correspondence: Bernhard Kreymann, II. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany.
Tel: 49 89 41402233. Fax: 49 89 41404878.
e-mail: Bernhard.Kreymann@lrz.tum.de

grade III and IV hepatic encephalopathy, irrespective of the underlying liver disease (14,15). In these patients, haemodialysis is performed with a modified polyamide haemodialyser and an albumin-containing dialysate which is recycled in a closed loop containing a charcoal cartridge, an anion exchanger resin adsorber, and a conventional haemodialyser (14,15). With dialysis using an albumin-containing dialysate, protein-bound substances which are usually not sufficiently dialysable can be eliminated (14,15).

Copper is strongly bound to caeruloplasmin; circulating copper is also loosely bound and transported by albumin. This small blood pool constitutes the so-called free copper in healthy subjects and is greatly elevated in patients with fulminant Wilson disease. We hypothesised that this pool of free copper, the pathogenetic factor of fulminant Wilson disease, could be removed by albumin dialysis and that the detoxification function of the liver would be supported by the same method. The method of Stange et al. is not suitable for this purpose because the charcoal cartridge and the anion exchanger resin adsorber do not remove copper from the circulating albumin-containing dialysate. Therefore, recycling of the albumin-containing dialysate was not applicable.

For this reason we based our new approach (albumin dialysis) on a slow albumin dialysate flow rate (1–2 l/h) which does not require the recycling of the albumin-containing dialysate. Our intention was to achieve stability in a patient with fulminant Wilson disease, enabling the recovery of liver function or bridging to liver transplantation.

Case Report

Two days before hospital admission, an 18-year-old male noticed that his urine had darkened and that he had developed progressive jaundice. His medical and family histories were negative, also lacking liver or renal disease.

After 5 days he was transferred to another hospital due to hyperacute liver failure, Coombs-negative haemolytic anaemia, and incipient kidney failure. Because of progressive liver failure, plasmapheresis was performed in this hospital.

Two days later he was transferred to the intensive care unit of our hospital because of suspected intoxication with an unknown drug. The diagnosis of Wilson disease was made in view of the following: the patient's age, the presence of haemolytic anaemia and hyperacute liver failure which presented with a low level of alkaline phosphatase, only minor increases of the transaminases, and high total bilirubin blood levels. The diagnosis was confirmed by highly elevated values of copper in serum (621 μg/dl, normal range 70–152 μg/dl) and urine (4968 μg/day, normal range <100 μg/day). Caeruloplasmin levels were not reliable as the patient had already been treated with plasmapheresis and transfusions of fresh-frozen plasma.

Hyperacute liver failure then developed with encephalopathy, haemolytic anaemia, and progressive renal failure. The patient furthermore showed lactic acidosis, acute pancreatitis, rhabdomyolysis, hepatosplenomegaly, and thrombocytopenia. Full supportive intensive care was instituted and therapy with D-penicillamine (1800 mg/day) and antioxidant therapy with g alpha tocopherol (100 mg/day) and acetylcysteine (50 mg/kg of body weight) were started. Two days after admission he suffered oligo-anuric renal failure and conventional continuous arterio-venous haemodiafiltration (CAVHDF) using an AN 69 dialyser (Hospal®, Nürnberg, Germany) was introduced. Only a total of 17 mg of copper was removed. Despite this treatment, hepatic encephalopathy progressed further to grade III (West Haven Criteria (16)), bilirubinaemia increased to 105 mg/dl and the serum copper level to 760 μg/dl. Liver transplantation could not be performed because of multiorgan failure. We therefore started albumin dialysis.

Blood values (normal range) at the beginning of the treatment were: total bilirubin (<1.2) 105 mg/dl; alkaline phosphatase (60–180) 94 U/l, aspartate aminotransferase (<18) 181 U/l, alanine aminotransferase (<23) 10 U/l, lactate (<2.4) 8.5 mmol/l, prothrombin time (13–17 s) 35 s, lactate dehydrogenase (80–240) 2700 U/l, creatinine kinase (<80) 3300 U/l, lipase 2207 (<80) U/l, creatinine (<1.3) 6.3 mg/dl, urea nitrogene (7–18) 83 mg/dl, haemoglobin 9.5 g/dl (14–18), platelet count (140 000–440 000) 115 000 per mm^3.

Methods

Because removal of copper by charcoal cartridge and the bilirubin adsorber as used by Stange et al. was not possible, we decided not to recycle the albumin solution. Instead, we performed bedside haemodialysis using an albumin dialysate as described below. *Bedside monitor:* bm 25 (Baxter® München, Germany), dialyser HF 80 (polysulfone membrane, Fresenius® Bad Homburg, Germany). *Dialysate:* SH 44-Hep (Schiwa® Glandorf, Germany) bicarbonate buffered 4.5-litre bag, 1 litre was replaced by 1 litre of 20% human albumin solution, resulting in a 44 g/l albumin concentration. The applied technique is similar to routine continuous veno-venous haemodiafiltration. Differences are the composition of the dialysate and the treatment time. The copper concentration of this fresh dialysate was 8.5 μg/dl±2 (mean±SEM, n=6) as hu-

man albumin is always loaded with trace elements such as copper which are not removed during its processing. Blood flow during the first six treatments was 140 ml/min, then increased to 200 ml/min. The ultrafiltration rate was set at an average of 0.4 l/h. For the first six treatments a femoralis arterio-venous access was used. In the consecutive treatments a double-lumen jugularis dialysis catheter was inserted. Low-dose heparin was administered for anticoagulation. The first six treatments used 22.5 litres of dialysate daily. In the first four treatments the dialysate flow rate was 2 l/h and treatment was completed after 11 h. During the first 2 nights CAVHDF was reinstituted. The protocol was then changed using a dialysate flow of 2 l/h for the first 13.5 litres and a dialysate flow rate of 0.6 l/h for the following 9 litres, increasing the treatment time to 23 h/day. After 7 days of treatment we reduced the amount of dialysate. During 20 treatments, 9 litres of dialysate were used at a flow rate of 1 l/h and during another 15 treatments, 4.5 litres were used at a similar flow rate.

During this period clinical condition, copper and bilirubin serum levels were used to decide whether albumin dialysis had to be performed. The aim was to prevent recurrence of multi-organ failure by keeping the copper blood level at least in the upper normal range and the bilirubin serum concentration under 40 mg/dl as the patient had no sign of hepatic encephalopathy at this bilirubin blood level.

Blood levels of other cations such as phosphate, magnesium, calcium and the trace element zinc were regularly controlled to see if albumin dialysis might cause an undesirable deficiency of these substances.

All laboratory results were obtained by routine chemical laboratory methods. Total bilirubin and copper were measured in all dialysates and the daily amount removed was then calculated. The copper content of the clean dialysate was subtracted. Fully informed consent was obtained from the patient if he was still legally capable and otherwise from his parents.

Results

The amount of copper removed per day is shown in Fig. 1. A total of 105 mg was removed during the first six treatments. The serum copper concentration fell to the normal upper blood concentration on day 7 (Fig. 1). A total of 16.1 g of total bilirubin was removed; daily removal is shown in Fig. 1. Hepatic encephalopathy (16) improved from grade III to 0 within 2 days of treatment. The EEG improved from grade II–III hepatic encephalopathy to an EEG showing no more slow-wave activity. Handwriting improved from illegible to legible within 2 days. The content of the text

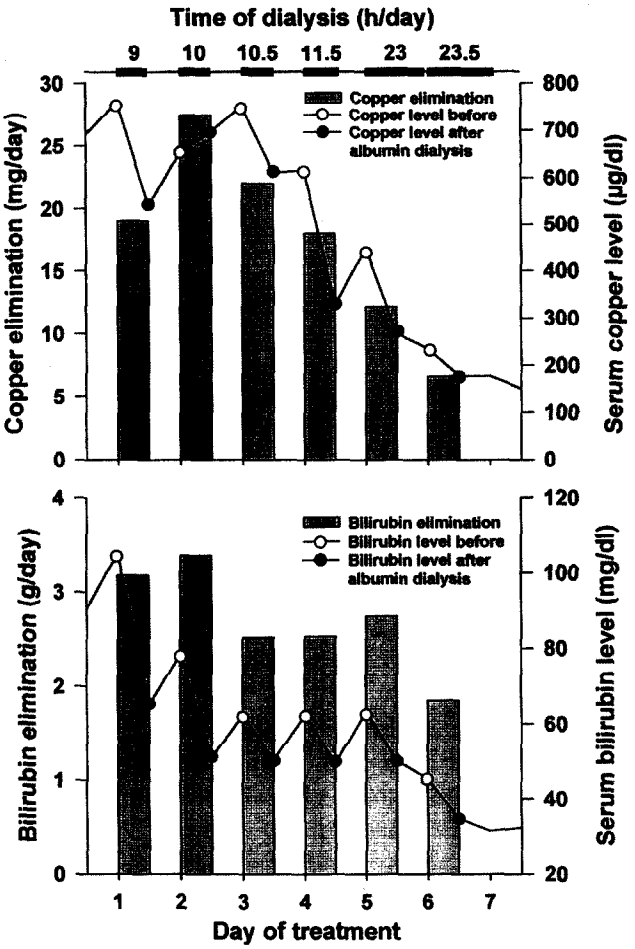

Fig. 1. Copper and bilirubin serum levels during the first 6 days of treatment. The bars indicate the total amounts of copper and bilirubin elimination. The line on the top graph shows the time span of albumin dialysis.

also demonstrated the return of the patient's cognitive function. After the fourth treatment, blood levels of creatine kinase and lactate were normalised, indicating control of rhabdomyolysis and lactic acidosis. After the sixth treatment the renal function returned, producing of 1 litre of urine/day and progressing to polyuria. Haemolysis was also arrested and LDH blood level fell to 501 U/l after the first six treatments. Lipase blood levels were significantly reduced, indicating improvement of pancreatitis. However, thrombocytopenia progressed further and led to nasal bleeding. The patient therefore required platelet transfusion, blood transfusion, and fresh-frozen plasma on the seventh day after starting the albumin dialysis.

After the improvement of the patient's condition, liver transplantation was suggested to him but he refused initially. Eventually, he agreed to liver transplantation and was placed on the waiting list. During this

period, 35 treatments were applied. A total of 27.5 g bilirubin was removed. The time course of copper and bilirubin blood levels and the amounts of copper and bilirubin removed by each treatment are shown in Fig. 2.

Serum levels of phosphate, magnesium, calcium and the trace element zinc were in the lower normal range during the treatment and no substitution of either substance was necessary; nor did clinical signs of a deficiency of any of these substances occur during albumin dialysis.

Sixteen days after starting albumin dialysis the kidney function was normal again and D-penicillamine therapy (900 mg/day) was reintroduced. Despite increased cupriuresis, blood values of copper and of bilirubin increased again. This required a more intensified dialysis protocol, which lowered bilirubin and copper blood levels (Fig. 2). On the 41st day after starting albumin dialysis D-penicillamine was changed to trientine (1800 mg/day), which effectively increased cupriuresis.

Without treatment, stabilisation of bilirubin blood levels was only achieved for a short period (days 16 to 26) despite removal of 455 mg of copper (240 mg by cupriuresis, 195 mg by albumin dialysis, and 20 mg by CAVHDF). By this time, the patient had a Karnofsky index of 90% and was allowed to go home for weekends. No improvement in liver functions was observed and the patient therefore required a total of 128 units of fresh-frozen plasma. Fifty-nine days after the start of albumin dialysis the patient underwent an orthotopic liver transplantation.

The copper concentration in a sample of the patient's explanted liver was 54.2 μg/g dry weight.

Three years after liver transplantation the patient is in very good health and has finished school.

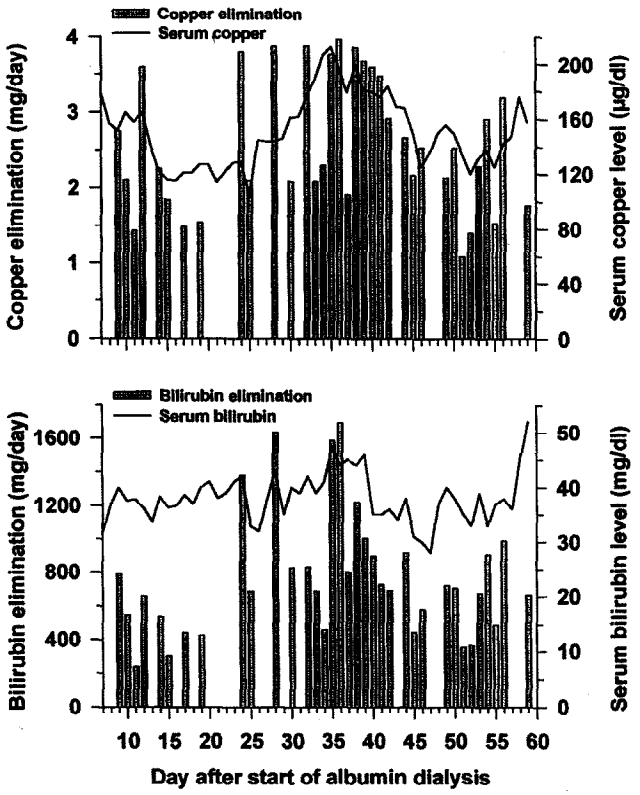

Fig. 2. Serum levels of copper and bilirubin until liver transplantation was performed. The bars show the amounts of copper and bilirubin eliminated by albumin dialysis and also indicate when an albumin dialysis was performed.

Discussion

Our patient presented with fulminant Wilson disease in combination with multiorgan failure. Multiorgan failure is one of the relative contraindications for urgent liver transplantation (17). Therefore, albumin dialysis was attempted with the aim of removing copper in order to improve liver and multiorgan failure. Simultaneously we hoped to improve hepatic encephalopathy and to treat uraemia. After recovery of the kidney function we were able to start a short-term trial with medical maintenance therapy for removal of copper. When stabilisation of liver function cannot be achieved at this stage, liver transplantation is required, as proposed by Schilsky et al. for patients with fulminant Wilson disease (9). However, we did manage to delay liver transplantation after control of multiorgan failure.

No similarly severe case of fulminant Wilson disease presenting with multiorgan failure and such high copper and bilirubin blood levels who survived, to our knowledge, has yet been described in the literature. Therefore, albumin dialysis would seem to offer a new treatment possibility for the removal of protein-bound toxic substances. Two-thirds of normal total copper body content (18) were removed by the first six treatments. Due to the rapid removal of the underlying pathogenetic toxin, the outcome of multiorgan failure may also have been positively influenced.

As a second marker of protein-bound substances we measured bilirubin elimination. A mean of 2.7 g bilirubin could be removed daily during the acute phase of treatment, which constitutes approximately 10 times the daily physiological production of bilirubin (19). In our patient CAVHDF was far less successful in the elimination of copper. Albumin dialysis for the removal of a protein-bound toxins can be improved with increased dialysate flow rate, continuous treatment from the beginning or increasing the albumin dialysate concentration.

Thrombocytopenia might be a side-effect attributable to albumin dialysis. The decreased antioxidant level could increase the vulnerability of the platelets, either during mechanical interactions with the blood pumps or during contact with the membrane of the dialyser. But thrombocytopenia could also be a side-effect of penicillamine treatment or due to the prolonged toxic effect of copper, as platelet transfusion was not required during the maintenance period.

A more intensive antioxidant treatment as suggested by Balistreri (20) might have diminished the number of albumin dialysis treatments during the maintenance period.

An earlier treatment with trientine could have prevented the increase of copper concentrations during the maintenance period. The use of another anticopper agent, ammonium tetrathiomolybdate which rapidly reduces the toxic nonceruloplasmin copper (21), might also have reduced the amount of albumin dialysis necessary during the maintenance period. But studies directly comparing the efficacy of the three anticopper agents (ammonium tetrathiomolybdate, trientine and penicillamine) are currently not available.

To date, Stange et al. have published 14 patients with acute or acute on chronic liver failure with grade III and IV hepatic encephalopathy using MARS. All patients improved and some could be bridged to liver transplantation (14,15). In a pilot study our method also seemed to be useful for patients with hepatic encephalopathy caused by liver diseases from other etiologies (22).

The albumin dialysis described above has several advantages in addition to those of MARS. We succeeded in performing a relatively simple bedside haemodiafiltration that can easily be used in any intensive care unit and that is relatively inexpensive and easy to construct. Toxin elimination is not limited by the binding capacity of the charcoal cartridge, nor the bilirubin adsorber, nor the circulating albumin solution. The treatment dose can be adjusted according to the patient's condition and can be extended to continuous, 24-h use. The amount of toxin removed can also be accurately measured.

Albumin dialysis can also be used as a time-limited extracorporeal detoxifying liver support. On a daily basis it was possible to remove about twice the normal bilirubin production. The histology of the excised liver showed complete cirrhosis and few hepatocytes. During albumin dialysis, hepatic encephalopathy did not recur, although there was no improvement in the liver synthesis function. This indicates that, at least for a limited period of time (59 days), the detoxification function of the liver can be supported using albumin dialysis. The longest treatment period by means of an extracorporeal liver assist device (ELAD) was 7 days using living liver cells (23). ELAD and other hybrid organ systems partially replace the liver synthesis function in addition to performing detoxification. However, the life span and performance of the liver cells are rather low to date. In our patient, the elevated serum copper level would probably have further limited the function of these cells. Furthermore, we cannot expect that the use of extracorporeal hybrid liver support systems, MARS, and extracorporeal liver perfusion will be available except in very specialised liver units in the near future. In comparison, albumin dialysis is a relatively simple bedside method and less expensive than ELAD.

The longer the liver failure continues, the more progressive muscle atrophy occurs, a sign of a disturbed protein metabolism. The risk of infection also increases with time. Therefore, the time in which conditions are favourable for transplantation is limited. On the other hand, liver transplantation is still accompanied by a 1-year mortality rate of at least 10–20% and lifelong immunosuppressive therapy is mandatory in most cases (24). It is also known that approximately 20% of liver transplantations due to hyperacute liver failure are in fact not necessary and thousands of patients are still dying on the waiting list according to UNOS (25). Albumin dialysis hopefully carries the promise of developing into a method which will allow discrimination between relative and absolute indications for liver transplantation. Using this new effective method of copper elimination, it seems that patients with severe fulminant Wilson disease can be bridged until liver transplantation is possible.

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