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Original Article

Dialysis in neonates with inborn errors of metabolism

Franz Schaefer, Emine Straube, Jun Oh, Otto Mehls and Ertan Mayatepek

Divisions of Pediatric Nephrology and Metabolic Diseases, University Children's Hospital, Heidelberg, Germany

Abstract

Background. Certain inborn errors of metabolism become manifest during the neonatal period by acute accumulation of neurotoxic metabolites leading to coma and death or irreversible neurological damage. Outcome critically depends on the immediate elimination of the accumulated neurotoxins. Recent technological progress provides improved tools to optimize the efficacy of neonatal dialysis.

Methods. We report our experience with continuous venovenous haemodialysis (CVVHD) in six neonates with hyperammonaemic coma due to urea-cycle disorders or propionic acidaemia and in one child with leucine accumulation due to maple-syrup urine disease (MSUD), in comparison with five patients managed by peritoneal dialysis (PD) (2 hyperammonaemia, 3 MSUD). Application of a new extracorporeal device specifically designed for use in small children permitted the establishment of stable blood circuits utilizing small-sized catheters, and the tight control of balanced dialysate flows over wide flow ranges.

Results. Plasma ammonia or leucine levels were reduced by 50% within 7.1 ± 4.1 h by CVVHD and within 17.9 ± 12.4 h by PD ($P < 0.05$). Also, total dialysis time was shorter with CVVHD (25 ± 21 h) than with PD (73 ± 35 h, $P < 0.02$). A comparison of the CVVHD results with published literature confirmed superior metabolite removal compared to PD, and suggested comparable efficacy as achieved with continuous haemofiltration techniques. Apart from accidental pericardial tamponade during catheter insertion in one case, no major complications were noted with CVVHD. In three of the five PD patients, dialysis was compromised by mechanical complications. None of the MSUD patients but four children with urea-cycle disorders died, two during the acute period and two later during the first year of life, with signs of severe mental delay. Of the eight children presenting with hyperammonaemic coma, the four with the most rapid dialytic ammonia removal rate (50% reduction in <7 h) survived with no or moderate mental retardation, whereas slower toxin removal was always associated with a lethal outcome. Simulation studies showed that the efficacy of neonatal CVVHD is limited mainly by blood-flow restrictions.

Conclusions. While CVVHD is the potentially most efficacious dialytic technique for treating acute metabolic crises in neonates, utmost care must be taken to provide an adequately sized vascular access.

Key words: ammonia; CVVHD; dialysis; leucine; metabolism; neonates

Introduction

Inherited dysfunctions of amino and organic acid metabolism usually become manifest in the early neonatal period by neurological abnormalities such as irritability, somnolence, and eventually coma [1–3]. In urea-cycle defects or in organic acidaemias, these symptoms are mainly due to excessive hyperammonaemia, which may cause irreversible neuronal damage [4,5]. In disorders of branched-chain amino acid (BCAA) metabolism such as maple-syrup urine disease (MSUD), prolonged accumulation of leucine and/or its metabolites (2-ketoisocaproic acid) may lead to severe permanent neurotoxicity [6].

During the past two decades, the prognosis of these previously lethal disorders has been considerably improved by the introduction of several therapeutic principles. Primarily, the generation of toxic metabolites can be suppressed by high calorie supply inducing a state of anabolism and reduced proteolysis. In hyperammonaemic disorders such as urea-cycle defects, lacking physiological or alternative pathway substrates can be infused to reduce ammonia concentrations. In MSUD, a diet with reduced BCAA contents can be instituted. Finally and most importantly, the accumulation of neurotoxic metabolites can be rapidly reversed by dialytic removal.

Historically, PD was shown to be of superior efficacy in urea-cycle disorders compared to the previously used exchange transfusions and pharmacological treatment alone [7,8]. More recently, extracorporeal blood purification is becoming increasingly attractive, since technological advances have improved the suitability of these techniques in neonates [9]. Superior efficacy

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Correspondence and offprint requests to: Dr F. Schaefer, Division of Pediatric Nephrology, University Children's Hospital, Im Neuenheimer Feld 150, D-69120 Heidelberg, Germany.
E-mail: franz_schaefer@med.uni-heidelberg.de

of continuous haemofiltration and intermittent haemodialysis in neonatal metabolic crises has been suggested in several case reports [9–20]. However, the experience with extracorporeal techniques in neonatal metabolic crises is still limited, and studies correlating the efficacy of neonatal rescue treatment with clinical outcome are lacking. In this study, we evaluated continuous venovenous haemodialysis (CVVHD) in comparison with PD in neonates with inborn errors of metabolism, and evaluated potential effects of the dialysis modality on long-term patient outcome.

Subjects and methods

Patients

The files of all patients with a biochemically proven inborn error of metabolism treated by dialysis for a first metabolic crisis during the first 4 weeks of life at Heidelberg University Children's Hospital between January 1988 and December 1997 were reviewed. Four patients with MSUD, three patients with propionic acidaemia (PA), and five patients with urea-cycle disorders (ornithine transcarbamylase deficiency (OTCD) ($n = 2$); carbamylphosphate synthetase deficiency (CPSD) ($n = 2$); argininosuccinate lyase deficiency (ASLD) ($n = 1$)) were identified.

Diagnosis of MSUD was confirmed by high plasma levels of leucine, isoleucine, valine and allo-isoleucine. The diagnosis of PA was made by increased urinary excretion of methylcitrate, propionylglycine, and other characteristic organic acids. In each case, the diagnosis was later confirmed by studies of propionyl-CoA carboxylase activity in cultured skin fibroblasts. Patients with CPSD were initially characterized by increased glutamine and alanine and decreased citrulline and arginine concentrations in plasma. Patients with OTCD were characterized by the same plasma amino acid pattern as found in CPSD but highly increased urinary orotic acid excretion. In both CPSD and OTCD, the diagnosis was subsequently confirmed by the assay of specific enzyme activity in liver tissue. ASLD was characterized by increased argininosuccinic acid concentrations in plasma and urine, and confirmed by enzyme studies in red blood cells.

The precise age and symptoms at initial presentation and at start of rescue therapy, details regarding dialysis and supportive medical treatment applied as well as the clinical and developmental status at last observation were recorded (Tables 1–3). Moreover, the time course of the blood concentrations of toxic metabolites (i.e. leucine in MSUD and ammonia in urea-cycle disorders and PA) during dialysis treatment was monitored by a median of 10 (range 5–25) metabolite measurements per patient.

Laboratory measurements

Ammonia was determined in EDTA plasma using glutamate dehydrogenase [21]. Plasma amino acids were measured by an automated ion-exchange chromatography with ninhydrine. Urinary organic acids were analysed by gas chromatography–mass spectrometry [22]. For the *in vitro* clearance study, leucine was measured by electrospray tandem mass spectrometry [23].

Supportive management of neonatal-onset metabolic derangement

General supportive care consisted of ventilatory and circulatory support as well as correction of electrolyte imbalances. A central venous catheter was placed immediately to ascertain good hydration and high energy supplementation. All protein intake was discontinued for the first 24 h. A hypercaloric parenteral nutrition with glucose at a rate of 20–25 g/kg/day with insulin at a low rate (0.05–0.1 IU/kg/h), lipids (1–2 g/kg/day) and electrolytes was infused.

In patients with urea-cycle disorders, sodium benzoate was given intravenously at a loading dose of 250 mg/kg over 2 h followed by a maintenance infusion of 250 mg/kg/day. In addition, intravenous L-arginine hydrochloride was administered at a starting dose of 2 mmol/kg within 2 h, followed by continuous infusion of 2 mmol/kg/day. Subjects with PA received intravenous L-carnitine at a dose of 200 mg/kg/day.

Dialysis

Between 1988 and 1993, peritoneal dialysis (PD) was primarily performed in patients with acute metabolic crises. Stylet catheters were placed percutaneously 3–5 cm below the umbilicus and midline in all patients. In one case, the catheter was replaced due to non-function by a surgically inserted single-cuff Tenckhoff catheter. PD was started using fill volumes of 15 to 30 ml/kg body weight (Table 2). Dwell times ranged from 30 to 60 min. Standard lactate-buffered solutions with glucose concentrations of 1.5 or 2.4% were used.

Since 1993, haemodialysis was performed *via* double-lumen catheters (5 French diameter/6.4 cm length, Medical Components Inc., Harleysville, USA) usually inserted into a femoral vein. A BM11 pump system was used for blood circulation (Baxter Dialysetechnik, Ettlingen, Germany) in connection with a BM14 double-peristaltic pump unit for controlling dialysis fluid flow. The integrated BM11/14 device, which became available in Germany in 1993, permits the maintenance of stable extracorporeal circuits at blood flow rates down to 5 ml/min, and to pass dialysis fluid safely at very constant rates of up to 100 ml/min along the dialyser. A bicarbonate-buffered electrolyte solution (HEP39, Braun-Schiwa, Glandorf, Germany) was used as dialysis fluid. As shown in Table 3, blood flow rates ranged between 10 and 30 ml/min, and dialysate flow rates of 1 to 5 l/h were chosen. Polysulphone dialysers (Spiraflo HFT02, filter surface area 0.2 m^2 (Bellco, Mirandola, Italy)) were used in five, cuprammonium dialysers (AM03, 0.3 m^2 (Asahi Medical, Frankfurt, Germany)) in two patients. The total volume of the extracorporeal system was 35–40 ml; the system was prefilled in all cases with blood in order to minimize haemodynamic effects of the extracorporeal circulation. Heparin was administered as a priming bolus of 1500 IU/m^2 followed by continuous infusion of 300–600 IU/m^2/h. Anticoagulation was monitored by hourly assessments of the activated coagulation time with a target range of 120–150 s.

Nutritional and medical management during maintenance period

All patients received protein-restricted diets which were nutritionally complete and met the requirements of vitamins, energy, and trace minerals for growth and normal development. MSUD patients received a low-protein diet with reduced BCAA contents aiming at maintaining plasma

Table 1. Patient characteristics, mode of treatment, and clinical outcome

Patient No.	Diagnosis	First symptoms	Age and symptoms at start of treatment	Initial marker concentration*	Dialysis modality	Age at last observation; Patient outcome
1	MSUD	5 d; poor feeding, drowsy	12 d; opisthotonic, convulsions	Leucine 3430 μmol/l	HD	1 year, moderate (mild?) motor delay, convulsions
2	MSUD	7 d; poor feeding	10 d; opisthotonic, convulsions	Leucine 2744 μmol/l	PD	4 years, moderate cognitive and motor delay
3	MSUD	6 d; poor feeding, drowsy	10 d; floppy, somnolence,vomiting	Leucine 2973 μmol/l	PD	5 years, hyperactive, moderate cognitive and motor delay
4	MSUD	6 d; floppy, jaundice	23 d; convulsions, respiratory insufficiency	Leucine 2897 μmol/l	PD	3 years, severe cognitive and motor delay
5	PA	7 d; poor feeding, somnolence	10 d; floppy; somnolence	Ammonia 2450 μmol/l	HD	2 years, normal development
6	PA	5 d; poor feeding, vomits, drowsy, floppy	7 d; convulsions, coma	Ammonia 1640 μmol/l	HD	3 years, moderate cognitive and motor delay
7	PA	lst wk; poor feeding	2 mo; convulsions, somnolence, dehydration, pancytopenia	Ammonia 1200 μmol/l	PD	4 years, normal cognitive development, moderate motor delay
8	OTCD	4 d; poor feeding, floppy, somnolence	5 d; somnolence, convulsions, respiratory insufficiency, pulmonary haemorrhage	Ammonia 930 μmol/l	HD	Died at age 8 d
9	OCTD	4 d; hyperexcitable, tachydyspnoeic	4 d; convulsions	Ammonia 1080 μmol/l	HD	Died at age 6 mo, severe motor delay
10	CPSD	3 d; opisthotonic, respiratory insufficiency	4 d; convulsions, respiratory insufficiency	Ammonia 3820 μmol/l	PD	Died at age 10 d
11	CPSD	6 d; poor feeding, somnolence	7 d; comatose	Ammonia 1800 μmol/l	HD	Died at age 9 mo, severe cognitive and motor delay
12	ASLD	5 d; poor feeding, floppy	8 d; respiratory insufficiency, comatose, convulsions, hypothermia, oliguria	Ammonia 1800 μmol/l	HD	4 years, moderate cognitive & motor retardation, convulsions

*Normal ranges: blood ammonia, <50 μmol/l; plasma leucine, <250 μmol/l. d, day; mo, month.

Table 2. Modalities and efficacy of continuous peritoneal dialysis. Cases are sorted by metabolite reduction time

Patient no.	Fill volume (ml/kg)	Dwell period (min)	Glucose concentration (g/dl)	Ammonia/leucine 50% reduction time (h)	Duration of dialysis (h)
7	17	30	1.5/2.4	6.5 (A)	15
10	30	30–60	1.5/2.4	7.1 (A)	110
3	33	60	2.4	16 (L)	72
2	15	30–60	1.5	24 (L)	80
4	45	60	2.4	36 (L)	88

BCAA at near normal concentrations. To this end, a BCAA-free amino-acid mixture (ILV-AM1/2 (SHS-Nutricia, Heilbronn, Germany) or MSUD1/2 (Milupa, Friedrichsdorf, Germany)), was used as a supplement to the cowmilk-based formula diet. The diet was based on leucine requirements (300–400 mg/day); isoleucine (150–200 mg/day) and valine (240–280 mg/day) were provided in proportion. In patients with PA an amino-acid mixture free of precursor amino acids (threonine, methionine, valine, and isoleucine) (IMTV-AM1–3 (SHS-Nutricia) or OS1/2 (Milupa)) was prescribed to meet the recommended daily allowance. Furthermore, carnitine was administered in oral doses of 100 mg/kg/day. In patients with urea-cycle defects, protein restriction was adjusted according to patient age and disease severity. Natural proteins were supplemented by an essential amino-acid mixture (E-AM1/2 (SHS-Nutricia) or UCD1/2 (Milupa)). Additional therapy included oral administration of sodium benzoate at maximum doses of 250 mg/kg/day, and oral L-arginine (100–200 mg/kg/day in CPSD and OTCD, 400 mg/kg/day in ASLD), aiming at plasma arginine concentrations of 100–200 μmol/l. Treatment was monitored regularly, with target ranges of <80 μmol/l for plasma ammonia and <800 μmol/l for plasma glutamine.

CVVHD efficacy study

A simulation study was performed in order to evaluate the effects of blood and dialysate flow on the efficacy of ammonia and leucine removal in the neonatal dialysis setting. To this end, the BM11/14 device was equipped with a neonatal tubing system and the Spiraflo HFT02 dialyser (0.2 m^2 surface area, Bellco, Mirandola, Italy). Two litres of an erythrocyte suspension were mixed with 20% human albumin solution to 50%

haematocrit and 60 g/l albumin concentration. Ammonium bicarbonate and leucine were added to final ammonia and leucine concentrations of 1500 µmol/l. The blood mixture passed through the extracorporeal circuit into a drainage bag. Blood flow was sequentially increased from 5 to 10, 15, 20, 30 and 50 ml/min. This sequence was repeated at dialysate flows of 1, 3, and 5 l/h. At each combination of blood and dialysate flow, blood samples were drawn from the inflow and the outflow lines after at least 120 ml had passed through the system to allow for equilibration. Ammonia and leucine clearances were calculated by the formula:

$$\text{Clearance (ml/min)} = \text{blood flow (ml/min)} * (C_{\text{pre}} - C_{\text{post}})/C_{\text{pre}}$$

where C_{pre} and C_{post} are the pre-and post-dialyser metabolite blood concentrations.

Statistics

All marker metabolite (i.e. ammonia or leucine) blood concentration values obtained between the start and the end of dialysis were used to fit a monoexponential decay curve given by the equation

$$C_{(t)} = C_{(0)} * e^{-k * t}$$

where C is the blood metabolite concentration, t is the duration of dialysis in hours, and k is the elimination coefficient. The time required to reduce the initial metabolite concentration by 50% was given by

$$t_{1/2} = ln2/k.$$

Non-parametric descriptive statistics were performed, using the Wilcoxon sign rank test to assess between-group differences. Significance was accepted for $P < 0.05$.

Results

Initial clinical presentation

As shown in Table 1, all patients developed symptoms of disease, usually starting with poor feeding behaviour and drowsiness, during the first week of life. A rapid deterioration of the neurological status followed, usually characterized by convulsions, somnolence, and coma. In all but two cases, a metabolic disorder was suspected shortly after onset of symptoms, and specific treatment was started within 1 week (median 3 days after first symptoms).

Efficacy of dialysis

Metabolite blood concentrations were efficiently lowered by combined dialysis and supportive medical treatment in all patients.

PD was apparently more efficient in the two patients with hyperammonaemia (50% ammonia reduction time 6.5 and 7.1 h) than in the three patients with MSUD (50% leucine reduction time 16–36 h) (Table 2, Figure 1). In one hyperammonaemic patient, rapid initial reduction was obtained but due to septicaemia and ongoing catabolism, blood ammonia levels remained between 120 and 200 µmol/l, necessitating maintenance PD for 4.5 days.

The dialysis modalities and efficacy of blood purification in the patients treated by CVVHD are given in Table 3. The 50% metabolite reduction times were significantly shorter with CVVHD than in the PD group as a whole ($P = 0.048$). The total duration of dialysis was also significantly shorter in the CVVHD than in the PD group ($P = 0.015$). A striking difference in dialysis efficacy was obvious in MSUD, where plasma leucine concentrations dropped approximately 10-fold more rapidly in the patient undergoing CVVHD than in the three subjects treated by PD. The reduction of blood ammonia in hyperammonaemic disorders appeared only slightly more efficient with CVVHD than with PD. The metabolite removal time was shortest in the two patients with the largest blood flow rates. In one patient on CVVHD (no. 5), blood ammonia levels reincreased to >200 µmol/l after termination of dialysis, so CVVHD was reinstituted for another 29 h. The results of the *in vitro* simulation study are shown in Figure 2. Up to a blood flow rate of 25 ml/min, the clearances of ammonia and leucine were a linear function of blood flow since extraction in the dialyser was close to 100%. At higher blood flows, extraction rates decreased and clearances became dependent on the dialysate flow rate.

Complications

In one case (no. 11) the haemodialysis catheter inserted *via* the right internal jugular vein perforated the right atrium, resulting in pericardial haemorrhage and circulatory failure. Prolonged cardiopulmonary resuscitation and surgical closure of the lesion were required, delaying effective dialysis by several hours. All other patients received catheters *via* femoral access without complications. Symptomatic thromboses of the punctured vein were not observed in any case.

The haemodialysis procedure was generally well tolerated; no major haemodynamic alterations or signs of dysequilibrium were noted after start of blood purification. One patient (no. 5) developed circulatory failure 6 h after the start of haemodialysis in association with signs of bacterial sepsis, necessitating cardiopulmonary resuscitation for a short period. CVVHD was continued immediately after the event without any further complications.

In the PD patients, obstruction and leakage of stylet catheters occurred in two cases each. In two patients the catheter had to be exchanged, once by another stylet and once by a Tenckhoff catheter.

Clinical response

Ten of the 12 patients showed clinical improvement shortly after start of dialysis. In these 10 patients, spontaneous movements were usually observed after few hours of dialysis, and mechanical ventilation could be stopped after a median of 21 h. Convulsions subsided in all except one MSUD patient who developed two additional seizures even after normalization of blood

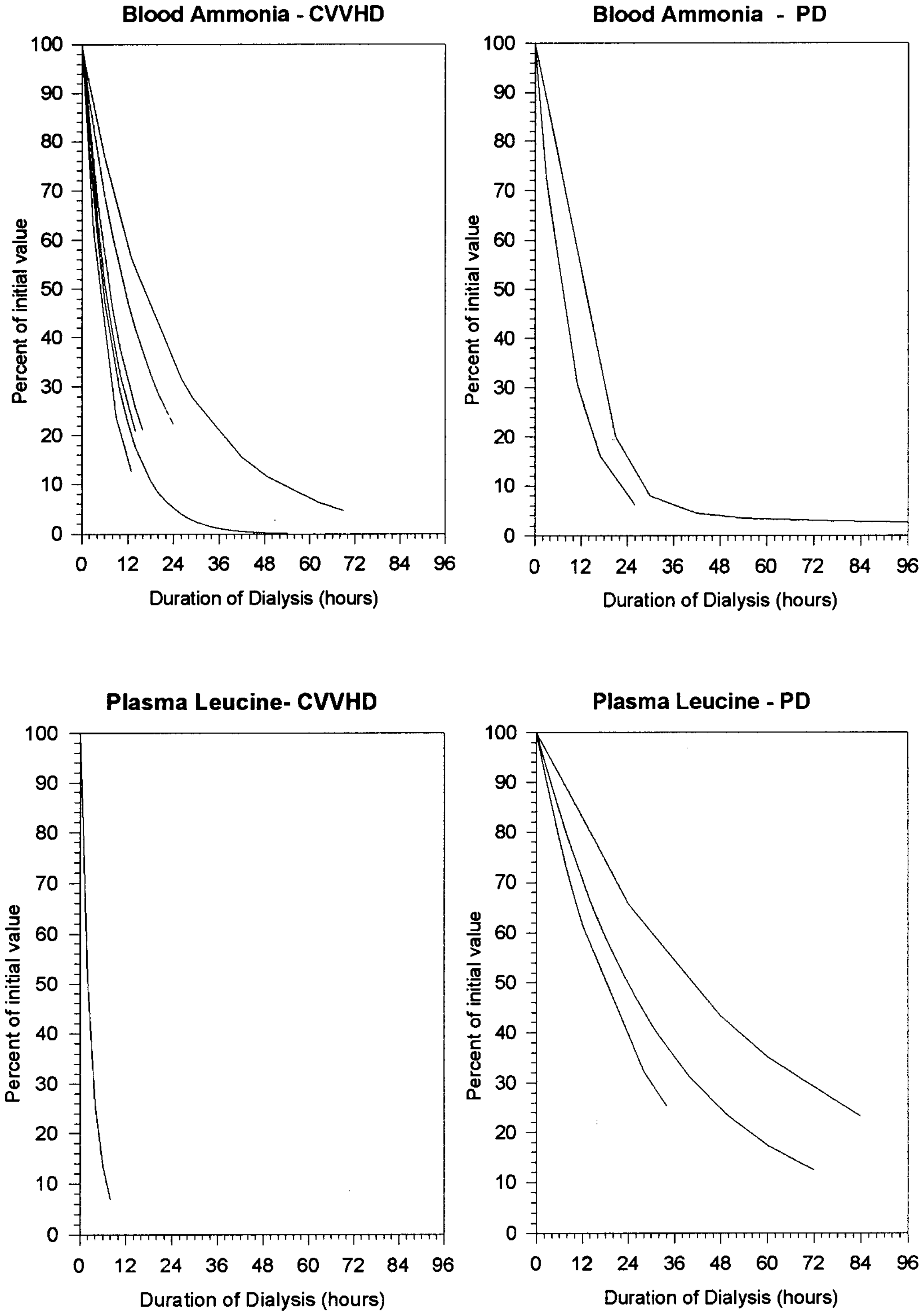

Fig. 1. Time course of marker metabolite elimination by dialysis in 12 neonates with acute metabolic crises. Upper row, blood ammonia; lower row, plasma leucine; left, CVVHD; right, PD.

leucine levels. One patient with OTCD (no. 8) did not show any clinical improvement despite normalization of blood ammonia levels, and all life-support treatment was stopped on the 4th day of coma when clinical examination and EEG indicated brain death. Another patient with CPSD treated by PD (no. 10) showed episodes of bradycardia and hypotension, followed by kidney and liver failure. In view of the disastrous clinical course, life support was stopped after 6 days of intensive care.

Table 3 Modalities and efficacy of continuous venovenous haemodialysis. Cases are sorted by metabolite reduction time

Patient no.	Blood flow (ml/min)	Dialysate flow (l/h)	Dialyser membrane	Ammonia/leucine 50% reduction time (h)	Duration of dialysis (h)
1	30	5	Spiraflo HFT02	2.1 (L)	12
12	40	1	AM03	4.4 (A)	12
5	10	1.5	Spiraflo HFT02	5.6 (A)	30
6	15	1.5	AM03	6.2 (A)	11
8	12	1	Spiraflo HFT02	7.1 (A)	16.5
9	15	3	Spiraflo HFT02	9.4 (A)	25
11	12	2	Spiraflo HFT02	15 (A)	71

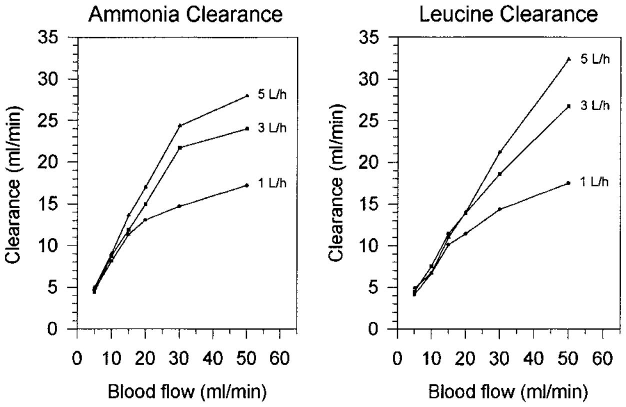

Fig. 2. Effect of blood and dialysate flow rate on ammonia and leucine removal by haemodialysis in a neonatal setting. See *Subjects and methods* for experimental protocol.

Patient outcome

Of the 10 patients surviving the neonatal metabolic crisis, two infants with urea-cycle defects died at 6 and 9 months of age after several periods of prolonged catabolism and metabolic derangement (Table 1). Since both patients, one of whom was the one with a history of pericardial tamponade and prolonged resuscitation, were already severely developmentally delayed, life-support measures were limited and no further attempt at active toxin removal by dialysis was made.

Of the three patients with neonatal hyperammonaemic crises due to PA, one showed completely normal cognitive and motor development, and two had moderate cognitive and/or motor deficits at the latest visit. In all children, the course of disease was characterized by frequent episodes of metabolic derangement triggered by acute catabolic states, usually due to minor infectious illnesses. These episodes are either self-limited or responsive to intravenous energy and insulin administration.

All children with MSUD survived, but developed moderate to severe cognitive and/or motor retardation during further follow-up. Recurrent seizures were observed in two children. An analysis of prognostic indicators for patient survival revealed a striking association between the efficacy of dialytic toxin removal and outcome. The four patients with hyperammonaemic coma in whom a 50% ammonia reduction time of less than 7 h was achieved survived with normal or moderately impaired neurodevelopment. In contrast, the four patients with a less rapid ammonia removal rate died either during the neonatal period or, with signs of severe retardation, during the later course of the disease. Notably, mean plasma ammonia concentrations at the start of treatment did not differ between survivors (1773 μmol/l) and non-survivors (1908 μmol/l). Similarly, the MSUD patient with the mildest neurodevelopmental impairment at last observation (no. 1) was the one with the most rapid leucine removal obtained by the use of CVVHD.

Discussion

While inborn errors of aminoacid and ketoacid metabolism have a relatively high prevalence and may manifest in the early neonatal period by lethal or permanently disabling metabolic crises, the diagnosis is frequently missed and few patients are referred to a specialized centre for life-saving emergency treatment of their metabolic derangement. In consequence, the collection of 12 cases reported here represents one of the largest single-centre experiences with neonatal metabolic crises treated by dialysis published to date. Furthermore, we provide the first systematic clinical evaluation of the CVVHD technique in neonates, a treatment modality which has been suggested in animal studies [24,25] and in a single case report [19] to be of superior efficacy compared to the conventionally used CVVH or PD. Finally, our study is the first to correlate the efficacy of dialytic toxin removal with long-term patient outcome.

Disorders causing neonatal metabolic crises

The most common forms of inborn errors of metabolism causing neonatal crises are MSUD, urea-cycle disorders, and propionic acidaemia. MSUD is a disorder of branched-chain ketoacid degradation. Particularly the accumulation of leucine and its metabolite, 2-ketoisocaproic acid, may cause acute brain dysfunction [1]. While patients with MSUD usually survive the neonatal period and appear healthy between episodes of metabolic imbalance, cognitive development is frequently subnormal. Propionic acidaemia (PA) is caused by propionyl-CoA carboxylase deficiency [2]. While the severity of the defect may differ between patients, those presenting as neonates with lethargy, feeding difficulties, and progressive encephalopathy have a high mortality rate, and severe neurological residua are frequent in survivors [5]. Hyperammonaemia is a constant finding in neonatal-onset PA, and ammonia is regarded as the main toxic metabolite responsible for severe and irreversible encephalopathy. A paradigm for the deleterious effects of ammonia on the neonatal brain is given by patients with urea-cycle disorders, who deteriorate rapidly with generalized muscular hypotonia, vasomotor instability, hypothermia, and apnoea and, if left untreated, usually die in coma with cerebral or pulmonary haemorrhage [26]. Severe hyperammonaemia is common to all forms of deficient urea synthesis. Ammonia induces various electrophysiological, vascular and biochemical alterations which altogether explain the clinical features of hyperammonaemia [3,27]. Because of the deleterious effects of leucine and its toxic metabolites in MSUD and of ammonia in PA and urea-cycle disorders, efficient removal of these substances is considered crucial in the emergency management of neonatal metabolic crises.

Dialysis efficacy in MSUD

In patients with MSUD, the low endogenous clearance of leucine and other branched-chain keto- and amino acids (BCAA) is insufficient to reverse the accumulation of BCAA that occurs during catabolic states. Since manifold higher BCAA clearance rates are achieved by PD, this technique has been regarded as the method of choice since its introduction in the 1980s [8,28,29]. More recently, 100–150% higher BCAA removal rates have been demonstrated experimentally with continuous extracorporeal blood purification techniques compared to PD [24]. In clinical practice, continuous arteriovenous [13] or venovenous haemofiltration [16,17,19], haemodialysis [19], and haemodiafiltration [19] have been shown to be feasible, but the efficacy achieved in the clinical setting was only slightly higher in the four published case reports where leucine clearance was measured [1.7–4.4 ml/min) [13,19] than in a single patient on PD whose leucine elimination rate was reported (0.9–3.4 ml/min) [28]. Also, the total duration of dialysis was only slightly shorter with extracorporeal (11–36 h [13,16,17,19]) than with PD (15–72 h [8,28,29]). In contrast, an exceptional leucine clearance (60 ml/min) with a 46% decrease of plasma leucine levels within 3 h was reported in a single case using intermittent haemodialysis [20].

In the MSUD patients presented here, the efficacy of PD was comparable to the published findings, with a 50% leucine reduction time of 16–36 h, and a total dialysis duration of 72–88 h. A markedly faster leucine elimination (50% reduction within 2.1 h) was obtained in a patient treated by CVVHD. Optimal technical conditions for CVVHD, with high blood and dialysate flow rates, were established in this patient. In the only other published case of MSUD treated by CVVHD, lower blood (20 ml/min) and dialysate flow rates (25 ml/min) were achieved [19]. Consequently, dialytic efficacy was lower than in the case presented here; the reported 81% decrease achieved within 12 h was accomplished in less than 5 h in our setting. Still, Jouvet *et al.* [19] found CVVHD to be of superior efficacy compared to the CVVH and CVVHDF techniques applied in two other children with MSUD. Blood flow limitations appear to determine the efficacy of leucine removal by CVVHD in the neonate. Our *in vitro* simulation study (Figure 2) clearly demonstrates that the full potential of CVVHD is only utilized when adequate blood flow rates are achieved.

Dialysis efficacy in hyperammonaemic disorders

In hyperammonaemic metabolic crises, the use of PD was reported in eight articles on a total of 23 patients, a continuous extracorporeal technique (mainly CVVH) was applied in nine cases published in seven papers, and intermittent haemodialysis was used in 15 patients summarized in five reports. A survey of this body of literature suggests that PD is of limited efficacy in hyperammonaemic patients, with normalization of blood ammonia levels in no less than 24 h, continued dialysis requirements over 1–5 days on average, and a failure to decrease ammonia levels in individual cases [7,8,10,11,15,29–31]. Better results were obtained using continuous haemofiltration, by which blood ammonia was typically reduced by >90% within 10 h and which could be stopped within 24 h [12–18]. The most efficient toxin removal was achieved by the use of intermittent haemodialysis, which reliably decreased blood ammonia concentrations by 75% within 3–4 h [9–11,18,20]. However, repeated haemodialysis sessions were usually required because of residual or rebound hyperammonaemia.

Hence, published literature confirms experimental findings [25] that ammonia is more efficiently removed by extracorporeal techniques than by PD. While haemodialysis is more efficient than haemofiltration both in the experimental setting [25] and according to clinical observation, correction of hyperammonaemia may be delayed using intermittent HD due to post-dialytic rebound. Hence, efficacy considerations and the advent of the the BM 11/14, an integrated device specifically designed for extracorporeal blood purification in small children, prompted us to use CVVHD in neonates presenting with hyperammonaemic crises. Up to now, six patients have been treated using this technique. Hyperammonaemia was successfully corrected in all patients; a minor rebound occurred in one case only. The rate of ammonia removal was satisfactory (>50% decrease within 12 h) in five of the six patients. The efficacy of toxin removal was better than that reported in literature for PD and comparable to that of continuous haemofiltration techniques, but lower than reported for intermittent haemodialysis. It should also be mentioned that the ammonia removal rates obtained by PD in two patients was in the same range as with CVVHD. Our simulation study demonstrates that in the given dialysis setting, ammonia clearance is a linear function of blood flow until blood flow rate exceeds 20 ml/min (Figure 2). Hence, the small calibres of the catheters used (5 French double lumen) precluded a more efficient use of CVVHD. Of note, all previous reports on CAVH, CVVH, or intermittent HD in neonates used 6.5 or 7 French double-lumen catheters or separate 5 and 8 French single-lumen catheters in the umbilical vessels.

Complications of dialysis

The choice of a dialysis technique in neonates with metabolic crises is influenced not only by efficacy, but also by safety considerations and the expected rate of complications. In three of the five PD patients the use of rigid stylet catheters was associated with obstruction and/or leakage, which required reduction of fill volumes, increase in inflow or outflow periods, and eventually exchange of the catheter, resulting in considerable delays of efficient toxin removal. These problems are seen less frequently with Tenckhoff catheters [32], which are now used in our unit. In CVVHD, vascular access was the greatest cause of concern. The use of the BM 11 blood pump permitted the use of 5 French double-lumen catheters, the smallest catheter size technically suitable for neonatal dialysis. While the complication rate can be expected to decrease with a smaller catheter calibre and no major thrombotic complications or haemorrhages from the puncture site were observed, the tragic case of a pericardial tamponade points to the considerable risks still inherent in central venous catheterization in critically ill neonates. Haemodynamic instability, another potential hazard of extracorporeal techniques in neonates, was efficiently prevented by prefilling the system with blood and using appropriate extracorporeal tubing and dialyser membranes with a total fill volume as small as 35 ml.

Outcome

All patients with MSUD survived the neonatal period. This is consistent with published literature, where 31 survivors were reported among 33 neonates dialysed for metabolic crises [8,13,16,17,19,20,28,29]. However, at the latest examination at 2–4 years of age, three of the four patients showed cognitive retardation, and all patients some degree of motor retardation. In view of the previously demonstrated inverse relationship between the duration of the neonatal metabolic derangement and intellectual outcome [6], it is of note that the patient in whom plasma leucine was normalized very rapidly by CVVHD was the only MSUD patient in whom a normal cognitive development was documented.

The prognosis of hyperammonaemic disorders is much less favourable than that of MSUD patients. Of the patients receiving neonatal dialysis reported in the literature, only 19 of 44 (43%) survived [7–12,14–18,20,29–31]. Msall *et al.* [4] reported severe neurological deficits in 26 patients with urea-cycle disorders surviving the first year of life. Cognitive performance was closely related to the duration of neonatal hyperammonaemic coma but not to the peak ammonia level. In keeping with the notion that the duration of neonatal hyperammonaemia is crucial for patient outcome, the four patients in this study in whom a very rapid toxin removal was achieved by dialysis survived with no or moderate developmental impairment, whereas those with a slower detoxification died either in the neonatal period or, with severe mental retardation, during further follow-up. In contrast, the initial blood ammonia concentration was not predictive of outcome, confirming the findings of Msall *et al.* [4].

With regard to the close relationship between the rate of toxin removal and outcome, our findings permit the conclusion that the most efficient dialysis modality should be used in neonates with hyperammonaemic coma, irrespective of the risks of the technique. Theoretical considerations and experimental results suggest that CVVHD should be the most efficient dialysis modality for removing leucine and ammonia from the circulation; in our hands, its efficacy in neonates was mainly limited by blood flow restrictions caused by the use of small-lumen catheters. We therefore recommend to use CVVHD as the first choice treatment in neonatal metabolic crises, taking care that an adequately sized catheter is used.

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