J. Inherit. Metab. Dis. 25 (2002) 531–546

Emergency management of inherited metabolic diseases

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MS received 25.09.02 Accepted 16.10.02

Summary: Inherited metabolic diseases with acute severe manifestations can be divided into five categories: (1) disorders of the intoxication type, (2) disorders with reduced fasting tolerance, (3) disorders with disturbed energy metabolism, (4) disorders of neurotransmission and (5) disorders in which no specific emergency treatment is available. Diagnostic emergency laboratory evaluation should cover all differential diagnoses that are therapeutically relevant and should always include ammonia, glucose, lactate and acid–base status as well as testing the urine for ketones. These are indispensable for planning and conducting the first steps of metabolic emergency treatment and should be available within 30 min. According to the clinical situation and biochemical derangement, special metabolic investigations must be initiated in parallel. These include acylcarnitine profiling with tandem mass spectrometry (in plasma or dried blood spots) and analysis of amino acids in plasma and of organic acids in urine. The results of all laboratory investigations relevant to the diagnosis of metabolic disorders for which specific emergency therapy exists should be available within 24 h. There is general agreement with regard to some therapeutic strategies that are clearly explained by pathophysiology: in disorders with endogenous intoxication, anabolism must be promoted and specific detoxification measures initiated. In disorders with reduced fasting tolerance, administration of glucose at the rate of hepatic glucose production forms the basis of treatment. Correction of acidosis is a major goal in disorders with disturbed mitochondrial energy metabolism, while glucose supply may have to be limited. Many current therapeutic strategies are based on case reports and personal experiences at different metabolic centres. The aim of devising the 'best' management is often hampered by the lack of objective evidence of efficacy.

Emergency treatment of metabolic disorders consists of symptomatic treatment, which is applied regardless of the underlying disorder, and specific treatment requiring knowledge of the nature of the underlying disorder. In most metabolic disorders in which there is acute decompensation, the long-term outcome is inversely related to the time between the onset of symptoms and the start of specific emergency treatment. This often requires the initiation of therapy before the exact diagnosis is known, and rapid initiation of specific investigations. The gap between first symptoms and final diagnosis ranges from a few hours to several days or longer, even in well-equipped and organized metabolic centres. This time is often marked by uncertainty regarding therapeutic measures. As a general rule, the results of all laboratory investigations relevant to the diagnosis of metabolic disorders for which specific therapy exists should be available within 24 h.

Even with a known diagnosis, uncertainties exist about the management thought to be optimal. A number of therapeutic strategies are based on case reports and personal experiences, but controlled trials are lacking owing to the small number of patients with metabolic decompensations treated in each metabolic centre. This paper reviews current opinions on emergency treatment. It might be the basis for future collaborative studies required for devising optimal metabolic emergency treatment.

THERAPEUTIC CLASSIFICATION OF METABOLIC DISORDERS

Metabolic disorders with acute life-threatening presentation are numerous, but from the therapeutic point of view most of them can be categorized into one of five groups.

1. Disorders of the intoxication type

This group comprises urea cycle disorders, organic acidopathies, amino acidopathies, fatty acid oxidation defects (especially long-chain fatty acid oxidation defects), galactosaemia and hereditary fructose intolerance.

Pathogenesis: Intoxication is caused by ammonia, toxic organic acids or amino acids, toxic long-chain acylcarnitines/acyl-CoA esters or toxic carbohydrate metabolites. It can be triggered both by exogenous intake of the relevant dietary component (protein, fat, galactose, fructose) and by endogenous breakdown of protein or fat during episodes of catabolism.

Principles of therapy: The oral intake of toxic precursors must be stopped. The endogenous catabolism of protein or fat must be reversed in disorders of protein or fat degradation. Specific detoxification measures should be instituted if available.

2. Disorders with reduced fasting tolerance

This group includes disorders of glucose homeostasis (glycogen storage diseases, disorders of gluconeogenesis, congenital hyperinsulinism) and disorders in which

ketone bodies cannot be synthesized for use as alternative substrates once glycogen stores are exhausted (fatty acid oxidation defects, disorders of ketogenesis/ketolysis).

Pathogenesis: These disorders become symptomatic during episodes of prolonged fasting. Hypoglycaemia is the main symptom. Fatty acid oxidation defects may also show features of group 1 disorders (intoxication due to the formation of toxic acylcarnitines/acyl-CoA esters), and defects in long-chain fatty acid oxidation in particular are better included in group 1 for therapeutic reasons.

Principles of therapy: Glucose administration at the rate of the hepatic glucose production is basically sufficient to meet caloric demands in these disorders. Only in patients with congenital hyperinsulinism may the need for glucose be much higher and it must be adjusted individually.

There is no need to force anabolism in these disorders, as there is no intoxication due to catabolism. The exception in (long chain-) fatty acid oxidation defects has already been mentioned.

3. Disorders with disturbed mitochondrial energy metabolism

This group comprises defects of the pyruvate dehydrogenase complex and the respiratory chain.

Pathogenesis: The generation of chemical energy is disturbed.

Principles of therapy: Correction of acidosis is a major goal. Glucose supply has to be limited, especially in defects of the pyruvate dehydrogenase complex, because a high glucose supply may exacerbate lactic acidosis.

4. Disorders of neurotransmission

Acute emergency treatment is available in two disorders of neurotransmission: vitamin B_6- and folinic acid-responsive seizures.

Principles of therapy: In every newborn with epileptic encephalopathy a trial with i.v. pyridoxine and folinic acid should be performed.

5. Disorders with no specific emergency treatment available

There are many other metabolic disorders that may present with acute, often encephalopathic, manifestations (e.g. nonketotic hyperglycinaemia, sulphite oxidase deficiency) or that usually follow a chronic progressive course but may worsen during episodes of acute illness (e.g. congenital disorders of glycosylation, peroxisomal disorders). These disorders are not considered in this review.

CLINICAL PRESENTATION

A classical clinical presentation may lead to the correct diagnosis, but often neither age of manifestation nor leading symptoms allow a straightforward diagnosis.

Age of manifestation

In principle, each group of disorders has a 'typical' time of manifestation but, depending on genetic and environmental factors, most metabolic diseases can exhibit first clinical symptoms at any age.

1. Disorders of the intoxication type: Children with disorders of the intoxication type are typically born after an uneventful pregnancy and show a symptom-free period after birth. The accumulation of toxic metabolites usually takes several hours to days. The patient with a disorder of protein or fat catabolism typically develops symptoms in the first few days of life during the naturally occurring catabolic period, explaining the frequent manifestation of these disorders in this age group. Affected neonates begin to suck poorly and develop lethargy progressing to coma. Sepsis is a common diagnosis considered in this situation. After the neonatal period, catabolism is rare in the first months of life because the baby is usually growing rapidly and is hence anabolic. Exposure to infections tends to be limited, and maternal antibodies provide additional protection. Towards the end of the first year of life, however, catabolism is more likely to occur, and the risk of metabolic decompensation increases as a consequence of episodes of infection and protein-rich meals. Disorders with exclusively exogenous intoxication— galactosaemia and hereditary fructose intolerance—become manifest after intake of these substances.

2. Disorders with reduced fasting tolerance: These disorders become symptomatic when the intervals between meals become longer or in the case of limited glucose supply, e.g. when vomiting or anorexia result from intercurrent infection. A few patients may present in the neonatal period, but more often they come to attention in the second half of the first year, when nocturnal feeding is discontinued.

3. Disorders of disturbed energy metabolism: Because of the prominent lactic acidosis, perinatal asphyxia is a common initial diagnosis in affected neonates. In addition, the generalized lack of energy often impairs intrauterine growth and development.

4. Disorders of neurotransmission: Vitamin B_6- and folinic acid-responsive seizures typically present immediately after birth with an epileptic encephalopathy unresponsive to conventional therapy. Other inborn errors of neurotransmission presenting with a chronic progressive encephalopathy dominated by extrapyramidal symptoms, e.g. defects in the metabolism of biogenic amines, are not considered in this review.

Main clinical features

Some clinical features are considered to be particularly suggestive of metabolic decompensation. However, every symptom has a broad spectrum of differential diagnoses.

Encephalopathy: Symptoms of encephalopathy (irritability, seizures, lethargy, coma) may develop in most metabolic emergencies. This may be due to intoxication (group 1), hypoglycaemia (group 2), disturbed energy metabolism (group 3) or disorders of neurotransmission (group 4).

Hepatopathy: Hepatic involvement can again be found in many disorders. The classical disorders that lead to liver failure with coagulopathy are disorders of the intoxication type (group 1), for example galactosaemia, hereditary fructose intolerance and tyrosinaemia type I. However, hepatic involvement may also be present in disorders with reduced fasting tolerance (group 2), for example fatty acid oxidation defects and glycogen storage disorders, and in disorders with disturbed energy metabolism (group 3). Finally, liver dysfunction may also be secondary to asphyxia or sepsis and these cases may be accompanied by elevated levels of ammonia and lactate and hypoglycaemia, thus mimicking decompensation of a metabolic disorder.

Cardiac failure: Cardiac presentation may be caused by fatty acid oxidation defects, particularly long-chain fatty acid oxidation defects (group 1). Similarly, disturbed mitochondrial energy metabolism (group 3) and severe asphyxia may lead to cardiac failure.

These three main clinical features—encephalopathy, hepatopathy, cardiac failure—are suggestive of an underlying metabolic disorder, particularly when present in combination, but they are not specific. Several differential diagnoses must be considered that require a completely different treatment. Consequently, a high level of awareness and intuition is invaluable. It is important to carry out a broad range of investigations in order to uncover the correct diagnosis.

DIAGNOSTIC TESTS

The laboratory investigations in a possible metabolic emergency should include all features that are important for immediate therapeutic decision making and/or that may reveal characteristic alterations in the acute phase of the disease. Every intensive care unit should prepare a metabolic emergency set for the initial investigations.

Basic laboratory investigations: These can be performed in the routine clinical chemistry laboratory, and results should be available immediately (glucose, blood gases, ketones in urine) or at latest within 30 min (ammonia, lactate, blood count, CRP, electrolytes, ALT, AST, CK, creatinine, urea, uric acid, coagulation studies).

A thorough interpretation of these basic investigations permits a preliminary differential diagnosis and the initiation of therapy. Guidelines for interpretation are described in metabolic reference textbooks (Fernandes et al 2000; Hoffmann et al 2002; Nyhan and Ozand 1998a; Scriver et al 2001; Zschocke and Hoffmann 1999).

Specific metabolic investigations: These usually lead to the definitive diagnosis but require a specialized metabolic laboratory. Tandem mass spectrometry allows analysis of acylcarnitines and amino acids in plasma or dried blood spots within a few hours and thus the rapid diagnosis of fatty acid oxidation defects, disorders of organic acid and amino acid metabolism and some urea cycle disorders. The latter two groups of disorders may also be recognized by classical amino acid profiling in plasma. The analysis of organic acids in urine may identify abnormal metabolites that are diagnostic for organic acidopathies and fatty acid oxidation defects. Free fatty acids and ketone bodies (3-hydroxybutyrate) are especially important if acylcarnitine profiling by tandem mass spectrometry is not readily available. To avoid delays, these investigations should generally be ordered in parallel and results should be available within 24 h. Further investigations may have to be performed depending on the clinical picture and the results of the basic investigations; these may include serum or plasma levels of insulin, carnitine in plasma and/or urine, homocysteine, urinary orotic acid, or reducing substances in urine.

Post-mortem investigations: If a child is suspected to have died from an inborn error of metabolism, it is critical to preserve adequate samples for post-mortem analysis: urine, plasma and dried blood spots for the above-mentioned investigations; CSF for neurometabolic investigations; EDTA whole blood for DNA analysis; fibroblasts for enzymatic studies; as well as tissue biopsies (muscle, liver, kidney) (Hoffmann et al 2002; Zschocke and Hoffmann 1999).

EMERGENCY TREATMENT

In the critically ill patient, treatment must be started immediately—in the majority of cases before the definite diagnosis is known. It is therefore inevitable that the initial treatment will be to some extent nonspecific. Diagnostic progress allows stepwise specification of therapeutic measures. We propose the following procedure in a suspected metabolic emergency, bearing in mind that different metabolic centres may treat differently and that evidence supporting particular therapeutic strategies may be limited. Doses of drugs that are essential in the acute emergency treatment, and that therefore should be available in every intensive care unit, are listed in Tables 1 and 2.

First step: High supply of glucose

A glucose/electrolyte infusion can be started before any laboratory results are available. However, adequate samples for metabolic studies must be obtained first,

Table 1 Alternative pathway therapy in hyperammonemia

Drug	*Priming infusion* (90 min)	*Sustaining infusion* (24 h)
	To be given in glucose 10% 30 ml/kg or (older patients) 500 ml/m^2 The drugs are given in addition to daily fluid and caloric requirement.	
L-Arginine	1–2 mmol/kg (3–6 mmol/kg in ASS, ASL)[a]	1–2 mmol/kg (3–6 mmol in ASS, ASL)[a]
Sodium benzoate	250 mg/kg	250 mg/kg
Sodium phenylacetate	250 mg/kg	250 mg/kg
Sodium phenylbutyrate	3 × 100–200 mg/kg/d p.o.	

Modified from Nyhan and Ozand (1998a) See text for details.
[a]ASS, argininosuccinate synthetase deficiency, synonymously citrullinaemia; ASL, argininosuccinate lyase deficiency

because pathological metabolites may normalize quickly with therapy. This is particularly important in hypoglycaemia, when dried blood spots and serum samples must be stored for specific analyses (acylcarnitines, carnitine, glucose, insulin, free fatty acids and ketone bodies). The intake of all potentially toxic compounds (protein, fat, galactose, fructose) must be stopped. Glucose should be started via a peripheral i.v. line at 150 ml/kg per day of a 10% solution (~10 mg glucose/kg per min, providing an energy supply of ~60 kcal/kg per day). Overhydration is rarely a problem in metabolic crises, as they are mostly accompanied by some degree of dehydration.

- This therapy is usually sufficient for disorders with reduced fasting tolerance; their pathophysiological mechanisms are readily reversed by a glucose supply at the rate of hepatic glucose production (7–8 mg/kg per min in the newborn).
- It is often not sufficient in disorders with endogenous intoxication, which demand higher energy supply to promote anabolism and often also require specific detoxification measures.
- It is potentially dangerous in disorders with disturbed energy metabolism (especially pyruvate dehydrogenase complex deficiency) as a high glucose supply may enhance lactic acidosis; because of the rarity of this disorder and the poor long-term outcome, it is justified to start with a high glucose supply, provided that lactate and acid–base status are checked regularly.

Second step: Adaptation of therapy according to the results of the basic laboratory investigations

If the basic laboratory results and the clinical findings indicate a disorder causing *endogenous intoxication*, therapy must be intensified even without knowledge of the definitive diagnosis. Anabolism must be promoted and detoxification measures must be initiated.

Anabolism is a very important goal during the entire course of treatment. It is achieved predominantly by a further increase in the supply of glucose. The need to provide sufficient energy will usually require a central line. Insulin may be added

Table 2 Additional drugs used in metabolic emergencies (alphabetical order)

Drug	*Disorder*	*Dosage* (given in 3 doses if not indicated differently)
Betaine	Disorders of homocysteine metabolism	250 mg/kg per day p.o.
Biotin	Holocarboxylase synthetase deficiency	10–15 mg/day p.o.
	Biotinidase deficiency	
	Hyperlactacidaemia	
L-Carnitine	Organic acidurias	50–300 mg/kg per day i.v./p.o.
	Carnitine transporter defect	
	MCAD deficiency	
	Mitochondrial disorders	
Diazoxide	Hyperinsulinism	15 mg/kg per day p.o.
Folic acid	Disorders of homocysteine metabolism	15 mg/kg per day i.v./p.o.
Folinic acid	Folinic acid-responsive seizures	3–5 mg/kg per day i.v.
Glucagon	Hyperinsulinism	Bolus: 30–100 μg/kg (max. 1 mg), then 5–10 μg/kg per hour i.v.
Hydroxocobalamin	Methylmalonic aciduria	1 × 1–5 mg/day i.m./i.v.
	Disorders of cobalamin metabolism	
	Transcobalamin II deficiency	
	Disorders of homocysteine metabolism	
Insulin	All disorders with endogenous intoxication	Start with 0.05–0.1 U/kg per h
Methionine	Disorders of remethylation	100 mg/kg per day p.o
NTBC	Tyrosinaemia type I	1–2 mg/kg per day p.o.
Pyridoxine	Pyridoxine-responsive seizures	1 × 50 mg i.v.
	Disorders of homocysteine metabolism	100–500 mg/day i.v./p.o.
Riboflavin	Glutaric aciduria types I and II	150 mg/day i.v./ p.o.
	Hyperlactacidaemia	
Thiamin	Hyperlactacidaemia	150 mg/day i.v./p.o.; >3 years 300 mg/day

See text for details

to promote anabolism (Biggemann et al 1993; Wendel et al 1982). This therapy requires regular monitoring of blood sugar concentrations. Fat should not be given until a fatty acid oxidation defect has been excluded. Detoxification is most important in hyperammonaemia, where ammonia must be removed as quickly as possible. Neurological damage is primarily related to the duration and the severity of hyperammonaemia. L-Arginine is an essential amino acid in all disorders of the urea cycle (except arginase deficiency). It is administered together with sodium benzoate and/or sodium phenylacetate, which provide alternative pathways of nitrogen excretion by conjugation with glycine and glutamine, respectively. Enteral sodium phenylbutyrate is employed to provide a source of phenylacetate. There has been some debate whether sodium benzoate or sodium phenylbutyrate/phenylacetate should be used for detoxification of ammonia before the diagnosis is known because in organic acidopathies there is the theoretical risk of additional intramitochondrial coenzyme A depletion (Griffith et al 1989; Kalbag and Palekar 1988; Potempska et al 1984). However, in many metabolic centres these drugs are regularly used for the detoxification of ammonia in organic acidopathies (especially propionic aciduria), without apparent adverse effects (Petrowski et al 1987; Walter et al 1995).

Extracorporal detoxification may be required if ammonia concentration exceeds 400 μmol/L and/or if ammonia levels do not decrease adequately with conservative treatment. This is often the case in multiorgan failure as the alternative pathway therapy requires intact hepatic and renal function for the formation and excretion of conjugates. In any case of a neonate with hyperammonaemic coma, the dialysis team should be informed immediately. The method of choice depends on local availability and the experience of the medical staff. Continuous venovenous haemodialysis (Rutledge et al 1990; Schaefer et al 1999), haemofiltration (Falk et al 1994; Ring et al 1990; Thompson et al 1991a) and haemodiafiltration (Falk et al 1994) have been shown to be effective. Extracorporal membrane oxygenation has been used in driving haemodialysis and haemofiltration (Summer et al 1996). If management cannot be promptly organized locally, the patient should be transferred to a specialized centre.

Correction of metabolic acidosis with sodium bicarbonate should be done carefully in hyperammonaemia because of the risk of ammonia dissociation and toxicity. Carnitine is supplemented to compensate for secondary carnitine deficiency caused by urinary excretion of carnitine-bound organic acids (Chalmers et al 1984). If a long-chain fatty acid oxidation defect is suspected, administration of carnitine, at least as a bolus, is avoided in many centres because of imminent accumulation of toxic long-chain acylcarnitines and the risk of fatal cardiac arrhythmia.

Laboratory studies to monitor therapy: Because of the high glucose supply, lactate, glucose and acid–base status must be monitored closely, initially every 1–2 h. Electrolyte disturbances have to be corrected. Sodium serum concentration should be kept well above 135 mmol/L to avoid complications such as cerebral cedema. Potassium concentration may drop following benzoate or phenylbutyrate/phenylacetate administration and should be kept above 3.5 mmol/L. The optimal

management of hyperammonaemia requires frequent assessment of ammonia concentrations; these should decline below 200 μmol/L within 12–24 h.

Supportive care: Symptomatic treatment has to be continued. Ventilator or circulatory support may be required. Convulsions may require anticonvulsive medication. Antibiotic therapy is recommended in every patient because sepsis is an important consideration in differential diagnosis and may be present concomitantly, leading to further catabolism.

Third step: Specific therapy derived from the results of specific metabolic investigations

The results of the specific metabolic investigations often lead to the exact diagnosis. Once the underlying disorder is known, specific treatment can be started. The following are some fundamental aspects.

Energy supply: Energy supply must be adapted according to the underlying disorder.

In *disorders requiring anabolism* (group 1), glucose in combination with insulin is continued. As soon as a fatty acid oxidation defect is excluded, fat (2–3 g/kg per day) should be added to increase the caloric supply in disorders of protein catabolism (urea cycle disorders, organic acidopathies, amino acidopathies). Medium-chain triglycerides (2–3 g/kg per day) can be of advantage in long-chain fatty acid oxidation defects as a fuel for the compromised energy metabolism, especially in heart (Brown-Harrison et al 1996). Little is known about the absolute energy requirements during metabolic decompensation. Theoretically, at least the age-related recommended daily energy should be provided. Some information on energy metabolism in inborn errors of metabolism has been provided by indirect calorimetry (Feillet et al 2000; Bodamer et al 1997). Resting energy expenditure has been shown to increase at least 30–40% during metabolic decompensation (Bodamer et al 1997). On the other hand, resting energy expenditure in patients with disorders of propionate metabolism in a stable metabolic state has been shown to be reduced to about 80% of that predicted by the Schofield height and weight equation (Feillet et al 2000), and physical activity that accounts for 25–30% of total daily energy expenditure in children (Bodamer et al 1997) is minimal in the immobile patient. This might explain the clinical observation that the energy required to promote anabolism is often lower than expected (Nyhan et al 1998b). In particular, the anabolic effect of insulin (Wendel et al 1982) may spare some energy requirements. However, it may still be difficult to achieve anabolism because of reduced glucose tolerance and peripheral insulin resistance, especially in multiorgan failure and metabolic acidosis. Human growth homone has been useful in promoting anabolism in a variety of organic acidopathies (Marsden et al 1994). It may also be useful in the management of acute metabolic decompensation. The dose employed has been 0.05 mg/kg per day.

With high caloric intake, fluid intake must be balanced cautiously. Weight must be monitored, in the first days to control fluid intake, later in order to check whether anabolism has been achieved. As soon as possible, enteral nutrition should be started. Continuous enteral slow drip feeding via a nasogastric tube has been shown to be effective in this situation (Nyhan et al 1998b; Parini et al 1993). Ondansetron (0.15 mg/kg in 15 min i.v., up to 3 times daily) may be tried in cases of continuous vomiting.

In *disorders of group 2* (reduced fasting tolerance), it is sufficient to provide glucose at the rate of hepatic glucose production (7–8 mg/kg per min in the newborn). Only in patients with congenital hyperinsulinism may the need for glucose be much higher and it must be adjusted individually.

In *disorders of energy metabolism* (group 3) deterioration of lactic acidosis sometimes requires the limitation of glucose supply to 3–5 mg/kg per min; the early addition of fat may be beneficial (2–4–6 g/kg per day).

Protein restriction in disorders of protein catabolism: Protein must be added in time to allow for anabolism. In infants still in coma from hyperammonaemia, maple syrup urine disease or organic acidopathies, natural protein intake is sometimes restricted for longer than the 24–48 h usually thought to be optimal. Careful daily evaluation of plasma amino acid concentrations is indispensable in these circumstances because protein malnutrition will prolong catabolism. Natural protein is given as breast milk or as an infant formula. In the presence of gastrointestinal problems, an amino acid solution can be given intravenously. In urea cycle disorders, a synthetic mixture of essential amino acids helps to reduce nitrogen load. Initially 0.5–0.8 g/kg per day of protein equivalent are administered. The first aim is to meet the daily protein requirement. The individual protein tolerance must subsequently be tested. The initial requirement may exceed the recommended daily allowance as a consequence of rapid protein synthesis and catch-up growth. Low levels of threonine and other essential amino acids indicate the need for a higher protein supply.

A mixture of precursor free amino acids is therapeutic in the management of the acute metabolic crisis in maple syrup urine disease. Their use in the synthesis of body protein reduces the elevated plasma levels of leucine and the other branched-chain amino acids (Berry et al 1991; Nyhan et al 1998b; Thompson et al 1991b). In other organic acidopathies, the toxic metabolites are not recycled for protein synthesis. Hence the precursor free amino acid mixture will not help to overcome the metabolic crisis, and may even aggravate hyperammonaemia because of the additional nitrogen load. It should therefore be started only when catabolism has been reversed.

Some essential amino acids may have to be supplemented separately as they become rate-limiting for protein synthesis. This is often the case for isoleucine and valine in maple syrup urine disease.

Detoxification/administration of specific drugs: In disorders with endogenous intoxication, detoxification measures have to be continued. In *urea cycle disorders*,

L-arginine, sodium benzoate and sodium phenylacetate/phenylbutyrate are continued (Feillet and Leonard 1998). Measuring plasma levels of sodium benzoate is advised in the neonatal period, particularly in jaundiced infants (Green et al 1983); this analysis, however, is not available in most centres. The risk of toxicity of sodium benzoate and sodium phenylacetate/phenylbutyrate is considered to be low with the doses listed in Table 1, but with less successful therapy there may be exploration of larger doses. In addition to ammonia, plasma amino acids are used to monitor the process of detoxification, with a target concentration of glutamine below 800 μmol/L. Arginine levels should be kept above 80 μmol/L. In argininosuccinate lyase deficiency, high-dose L-arginine (6 mmol/kg per day) alone may be sufficient for detoxification. Citrate may be added to compensate for secondary loss of Krebs cycle intermediates. Because of this very effective treatment, extracorporal detoxification can usually be avoided in this disorder. Citrullinaemia may also require high doses of L-arginine. In ornithine carbamoyltransferase and carbamylphosphate synthetase deficiency, oral citrulline instead of L-arginine may be advantageous. In *N*-acetylglutamate synthetase deficiency, *N*-carbamylglutamate has become available as the treatment of choice. Carnitine may be discontinued unless there is secondary carnitine deficiency (Mori et al 1990; Ohtani et al 1988).

In *organic acidopathies*, carnitine treatment is maintained at 100–300 mg/kg per day. This restores free coenzyme A in the mitochondria and enhances the excretion of short-chain acylcarnitines (Roe et al 1984a). Serum levels of free carnitine should be in the upper normal range. Sodium bicarbonate may be required if metabolic acidosis is present but should be given carefully in hyperammonaemia. In severe hyperammonaemia (which may occur especially in propionic aciduria) arginine can be given to enhance urea cycle activity by activation of *N*-acetylglutamate synthetase (Kamemoto and Atkinson 1985), but depending on the level of ammonia, benzoate (Walter et al 1995) and phenylbutyrate or phenylacetate (Petrowski et al 1987) may also be required to lower ammonia. *N*-Carbamylglutamate may be effective in reducing hyperammonaemia in patients with methylmalonic and propionic aciduria (Gebhardt et al 2002).

There are some organic acidopathies in which cofactor treatment should be tried. Hydroxocobalamin should be tested in all cases of methylmalonic aciduria. Biotin is the treatment of choice in holocarboxylase synthetase deficiency and biotinidase deficiency. Riboflavin should be tried in glutaric aciduria types I and II. In any severe metabolic decompensation accompanied by insufficient food intake and severe lactic acidaemia, a trial with thiamin should be performed (Matern et al 1996; Mayatepek and Schulze 1999). In methylmalonic aciduria, forced diuresis and alkalinization of urine with sodium bicarbonate help to eliminate methylmalonic acid. In propionic and methylmalonic aciduria, metronidazole suppresses intestinal bacterial propionate production. In isovaleric aciduria and methylcrotonyl-CoA carboxylase deficiency, glycine can be used in combination with carnitine to promote the excretion of glycine conjugates. This is particularly useful for long-term treatment. In the emergency treatment, carnitine alone is adequate and is essential to compensate for secondary carnitine deficiency (Chalmers et al 1984; Roe et al 1984b).

Maple syrup urine disease may require extracorporal detoxification if leucine levels exceed 1500 μmol/L (20 mg/dl). As in hyperammonaemia, continuous arteriovenous or venovenous haemodialysis (Jouvet et al 1997; Rutledge et al 1990; Schaefer et al 1999), haemofiltration (Falk et al 1994; Ring et al 1990; Thompson et al 1991a) and haemodiafiltration (Falk et al 1994) have been shown to be effective. Each child with maple syrup urine disease should be assessed for response to thiamin (Fernhoff et al 1985). In *tyrosinaemia type I*, NTBC is the treatment of choice to prevent production of toxic metabolites.

Disorders accompanied by *hyperhomocysteinemia*, such as homocystinuria and disorders of methyl group transfer (including methylenetetrahydrofolate reductase deficiency), may require treatment with hydroxocobalamin, folic acid, pyridoxine, betaine or methionine, depending on the underlying enzymatic defect.

In *long-chain fatty acid oxidation defects*, caution is advised with regard to the administration of carnitine because of the risk of formation of toxic acylcarnitines, but severe secondary carnitine deficiency may require cautious oral carnitine substitution. Other disorders of fatty acid oxidation, including *carnitine transporter defect* and *MCAD deficiency*, may benefit from early supplementation of carnitine to compensate for primary or secondary carnitine deficiency and to promote the excretion of acylcarnitine esters.

The initial treatment of *hyperinsulinism* may require drug therapy with glucagon and/or diazoxide in addition to the high glucose supply (10–30 mg/kg per min).

In *congenital lactic acidaemia*, few strategies are of proven efficacy (Morris and Leonard 1996). A trial should be performed with thiamin (cofactor of pyruvate dehydrogenase complex), riboflavin (cofactor of complex I) and biotin (cofactor of pyruvate carboxylase). Secondary carnitine deficiency is treated with L-carnitine. Correction of metabolic acidosis with sodium bicarbonate, and if sodium level exceeds 160 mmol/L with trometamol, is essential.

In *neonatal epileptic encephalopathy*, a trial with pyridoxine and folinic acid should be performed. In suspected metabolic disorders, some drugs should be restricted to acute emergencies with no other effective drugs available because they may inhibit mitochondrial function; these include sodium valproate, chloralhydrate, chloramphenicol, tetracyclines and salicylates.

Final step: Precautions before discharging the patient from hospital

Once the patient with metabolic disorder is discharged from hospital, precautions must be taken regarding the avoidance and the management of impending decompensations. Parents must be aware of causes and early signs of metabolic derangement and should be taught how and when to initiate the first steps of emergency treatment at home (Dixon and Leonard 1992). Every patient should be supplied with an emergency card describing the individual procedure that has to be followed at home and in the primary care hospital where no metabolic specialist may be available. The in-hospital procedure is quite similar to what has been outlined above. Specific emergency treatment can of course be initiated immediately. Gastrostomy or nasogastric tube feeding allows for high-caloric enteral feeding and drug

treatment in the case of refusal to eat. A port-a-cath system may be very helpful and provides an immediate central line for emergency treatment.

CONCLUDING REMARK

This proposal is based on the results of several international workshops on emergency treatment (Hoffmann and Prietsch 2000; Prietsch et al 2001). It reflects current opinions on management of metabolic emergencies. However, there are still many open questions regarding emergency treatment. In the future, controlled multicentre trials are needed to devise optimized management of metabolic emergencies.

ACKNOWLEDGEMENTS

We thank Dr B. Sczcerbak, Milupa, Germany, for the co-initiative and help in organizing workshops on emergency treatment from the logistics to the necessary financial support, and Dr J. Leonard for his input through stimulating discussions and by reviewing the manuscript.

REFERENCES

Berry GT, Heidenreich R, Kaplan P, et al (1991) Branched-chain amino acid-free parenteral nutrition in the treatment of acute metabolic decompensation in patients with maple syrup urine disease. *N Engl J Med* **17**;324(3): 175–179.

Biggemann B, Zass R, Wendel U (1993) Postoperative metabolic decompensation in maple syrup urine disease is completely prevented by insulin. *J Inherit Metab Dis* **16**: 912–913.

Bodamer OA, Hoffmann GF, Visser GH, et al (1997) Assessment of energy expenditure in metabolic disorders. Eur J Pediatr **156** (Suppl 1): S24–28.

Brown-Harrison MC, Nada MA, Sprecher H, et al (1996) Very long chain acyl-CoA dehydrogenase deficiency: successful treatment of acute cardiomyopathy. *Biochem Mol Med* **58**(1): 59–65.

Chalmers RA, Roe CR, Stacey TE, Hoppel CL (1984) Urinary excretion of *l*-carnitine and acylcarnitines by patients with disorders of organic acid metabolism: evidence for secondary insufficiency of *l*-carnitine. *Pediatr Res* **18**: 1325–1328.

Dixon MA, Leonard JV (1992) Intercurrent illness in inborn errors of intermediary metabolism. *Arch Dis Child* **67**: 1387–1391.

Falk MC, Knight JF, Roy LP, et al (1994) Continuous venovenous haemofiltration in the acute treatment of inborn errors of metabolism. *Pediatr Nephrol* **8**: 330–333.

Feillet F, Leonard JV (1998) Alternative pathway therapy for urea cycle disorders. *J Inherit Metab Dis* **21** (Suppl 1): 101–111.

Feillet F, Bodamer OA, Dixon MA, Sequeira S, Leonard JV (2000) Resting energy expenditure in disorders of propionate metabolism. *J Pediatr* 136: 659–663.

Fernandes J, Saudubray JM, Van den Berghe G (2000) *Inborn Metabolic Diseases*, 3rd ed. Berlin: Springer.

Fernhoff PM, Lubitz D, Danner DJ, et al (1985) Thiamine response in maple syrup urine disease. *Pediatr Res* **19**: 1011–1016.

Gebhardt B, Vlaho S, Böhles H (2002) Enhanced ammonia detoxification by *N*-carbamylglutamate in a patient with decompensated methylmalonic aciduria. *34th European Metabolic Group Meeting*, Zürich, 2002, Abstracts, 61.

Green TP, Marchessault RP, Freese DK (1983) Disposition of sodium benzoate in newborn infants with hyperammonemia. *J Pediatr* **102**: 785–790.

Griffith AD, Cyr DM, Egan SG, Tremblay GC (1989) Inhibition of pyruvate carboxylase by sequestration of coenzyme A with sodium benzoate. *Arch Biochem Biophys* **15**;269(1): 201–207.

Hoffmann GF, Nyhan WL, Zschocke J, Kahler SG, Mayatepek E (2002) *Inherited Metabolic Diseases*. Baltimore: Lippincott Williams and Wilkins.

Hoffmann GF, Prietsch V (2000) Emergency treatment in inborn errors of metabolism. In: *Publication of Workshop Results, 32nd European Metabolic Group Meeting*, Hamburg, 2000, 22–25.

Jouvet P, Poggi, F, Rabier D, et al (1997) Continuous venovenous haemodiafiltration in the acute phase of neonatal maple syrup urine disease. *J Inherit Metab Dis* **20**: 463–472.

Kalbag SS, Palekar AG (1988) Sodium benzoate inhibits fatty acid oxidation in rat liver: effect on ammonia levels. *Biochem Med Metab Biol* **40***: 133–142.*

Kamemoto ES, Atkinson DE (1985) Modulation of the activity of rat liver acetylglutamate synthase by pH and arginine concentration. *Arch Biochem Biophys* **15**;243(1): 100–107.

Marsden D, Barshop BA, Capistrano-Estrada S, et al (1994) Anabolic effect of human growth hormone: management of inherited disorders of catabolic pathways. *Biochem Med Metab Biol* **52**: 145–154.

Matern D, Seydewitz HH, Lehnert W, Niederhoff H, Leititis JU, Brandis M (1996) Primary treatment of propionic acidemia complicated by acute thiamine deficiency. *J Pediatr* **129**: 758–760.

Mayatepek E, Schulze A (1999) Metabolic decompensation and lactic acidosis in propionic acidaemia complicated by thiamine deficiency. *J Inherit Metab Dis* **22**: 189–190.

Mori T, Tsuchiyama A, Nagai K, Nagao M, Oyanagi K, Tsugawa S (1990) A case of carbamylphosphate synthetase-I deficiency associated with secondary carnitine deficiency—L-carnitine treatment of CPS-I deficiency. *Eur J Pediatr* **149**: 272–274.

Morris AA, Leonard JV (1996) The treatment of congenital lactic acidoses. *J Inherit Metab Dis* **19**: 573–580.

Nyhan WL, Ozand PA (1998a) *Atlas of Metabolic Diseases*. London: Chapman and Hall.

Nyhan WL, Rice-Kelts M, Klein J, Barshop BA (1998b) Treatment of the acute crisis in maple syrup urine disease. *Arch Pediatr Adolesc Med* **152**: 593–598.

Ohtani, Y, Ohyanagi K, Yamamoto S, Matsuda I (1988) Secondary carnitine deficiency in hyperammonemic attacks of ornithine transcarbamylase deficiency. *J Pediatr*. **112**: 409–414.

Parini R, Sereni LP, Bagozzi DC, et al (1993) Nasogastric drip feeding as the only treatment of neonatal maple syrup urine disease. *Pediatrics* **92**: 280–283.

Petrowski S, Nyhan WL, Reznik V, et al (1987) Pharmacologic amino acid acylation in the acute hyperammonemia of propionic acidemia. *J Neurogenet* **4**: 87–96.

Potempska A, Loo YH, Wisniewski HM (1984) On the possible mechanism of phenylacetate neurotoxicity: inhibition of choline acetyltransferase by phenylacetyl-CoA. *J Neurochem* **42**: 1499–1501.

Prietsch V, Zschocke, J Hoffmann GF (2001) Diagnostik und Therapie des unbekannten Stoffwechselnotfalls. *Monatsschr Kinderheilkd* **149**: 1078–1090

Ring E, Zobel G, Stockler S (1990) Clearance of toxic metabolites during therapy for inborn errors of metabolism. *J Pediatr* **117**: 349–350.

Roe CR, Millington DS, Maltby DA, Bohan TP, Hoppel CL (1984a) L-Carnitine enhances excretion of propionyl coenzyme A as propionylcarnitine in propionic acidemia. *J Clin Invest* **73**: 1785–1788.

Roe CR, Millington DS, Maltby DA, Kahler SG, Bohan TP (1984b) L-Carnitine therapy in isovaleric acidemia. *J Clin Invest* **74**: 2290–2295.

Rutledge SL, Havens PL, Haymond MW, McLean RH, Kan JS, Brusilow SW (1990) Neonatal hemodialysis: effective therapy for the encephalopathy of inborn errors of metabolism. *J Pediatr* **116**: 125–128.

Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E (1999) Dialysis in neonates with inborn errors of metabolism. *Nephrol Dial Transplant* **14**: 910–918.

Scriver CR, Beaudet AL, Sly WS, Valle D, eds; Childs B, Kinzler KW, Vogelstein B, assoc. eds. (2001) *The Metabolic and Molecular Bases of Inherited Diseases*, 8th edn. New York: McGraw-Hill.

Summar M, Pietsch J, Deshpande J, Schulman G (1996) Effective hemodialysis and hemofiltration driven by an extracorporeal membrane oxygenation pump in infants with hyperammonaemia. *J Pediatr* **128**: 379–382.

Thompson GN, Butt WW, Shann FA, et al (1991a) Continuous venovenous hemofiltration in the management of acute decompensation in inborn errors of metabolism. *J Pediatr* **118**: 879–884.

Thompson GN, Francis DE, Halliday D (1991b) Acute illness in maple syrup urine disease: dynamics of protein metabolism and implications for management. *J Pediatr* **119**: 35–41.

Walter JH, Wraith JE, Cleary MA (1995) Absence of acidosis in the initial presentation of propionic acidaemia. *Arch Dis Child Fetal Neonatal Ed* **72**(3): F197–199.

Wendel U, Langenbeck U, Lombeck, I Bremer HJ (1982) Maple syrup urine disease—therapeutic use of insulin in catabolic states. *Eur J Pediatr* **139**: 172–175.

Zschocke J, Hoffmann GF (1999) *Vademecum Metabolicum. Manual of Metabolic Paediatrics*. Stuttgart: Schattauer.