Aktiv Druck & Verlag GmbH | ISSN 0170 - 5334 | 02330

www.ai-online.info

57. Jahrgang | November 2016

A&I

ANÄSTHESIOLOGIE & INTENSIVMEDIZIN

Offizielles Organ: Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V. (DGAI)
Berufsverband Deutscher Anästhesisten e.V. (BDA)
Deutsche Akademie für Anästhesiologische Fortbildung e.V. (DAAF)
Organ: Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin e.V. (DIVI)

Maple syrup urine disease

orphananesthesia

a project of the German Society
of Anaesthesiology and Intensive Care Medicine

SUPPLEMENT NR. 14 | 2016

orphananesthesia
a project of the German Society of Anaesthesiology and Intensive Care Medicine

www.orphananesthesia.eu

OrphanAnesthesia –

ein krankheitsübergreifendes Projekt des Wissenschaftlichen Arbeitskreises Kinderanästhesie der Deutschen Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

Ziel des Projektes ist die Veröffentlichung von Handlungsempfehlungen zur anästhesiologischen Betreuung von Patienten mit seltenen Erkrankungen. Damit will Orphan Anesthesia einen wichtigen Beitrag zur Erhöhung der Patientensicherheit leisten.

Patienten mit seltenen Erkrankungen benötigen für verschiedene diagnostische oder therapeutische Prozeduren eine anästhesiologische Betreuung, die mit einem erhöhten Risiko für anästhesieassoziierte Komplikationen einhergehen. Weil diese Erkrankungen selten auftreten, können Anästhesisten damit keine Erfahrungen gesammelt haben, so dass für die Planung der Narkose die Einholung weiterer Information unerlässlich ist. Durch vorhandene spezifische Informationen kann die Inzidenz von mit der Narkose assoziierten Komplikationen gesenkt werden. Zur Verfügung stehendes Wissen schafft Sicherheit im Prozess der Patientenversorgung.

Die Handlungsempfehlungen von OrphanAnesthesia sind standardisiert und durchlaufen nach ihrer Erstellung einen Peer-Review-Prozess, an dem ein Anästhesist sowie ein weiterer Krankheitsexperte (z.B. Pädiater oder Neurologe) beteiligt sind. Das Projekt ist international ausgerichtet, so dass die Handlungsempfehlungen grundsätzlich in englischer Sprache veröffentlicht werden.

Ab Heft 5/2014 werden im monatlichen Rhythmus je zwei Handlungsempfehlungen als Supplement der A&I unter www.ai-online.info veröffentlicht. Als Bestandteil der A&I sind die Handlungsempfehlungen damit auch zitierfähig. Sonderdrucke können gegen Entgelt bestellt werden.

Bisher in A&I publizierte Handlungsempfehlungen finden Sie unter:

www.ai-online.info/Orphsuppl
www.orphananesthesia.eu

OrphanAnesthesia –

a common project of the Scientific Working Group of Paediatric Anaesthesia of the German Society of Anaesthesiology and Intensive Care Medicine

The target of OrphanAnesthesia is the publication of anaesthesia recommendations for patients suffering from rare diseases in order to improve patients' safety. When it comes to the management of patients with rare diseases, there are only sparse evidence-based facts and even far less knowledge in the anaesthetic outcome. OrphanAnesthesia would like to merge this knowledge based on scientific publications and proven experience of specialists making it available for physicians worldwide free of charge.

All OrphanAnesthesia recommendations are standardized and need to pass a peer review process. They are being reviewed by at least one anaesthesiologist and another disease expert (e.g. paediatrician or neurologist) involved in the treatment of this group of patients.

The project OrphanAnesthesia is internationally oriented. Thus all recommendations will be published in English.

Starting with issue 5/2014, we'll publish the OrphanAnesthesia recommenations as a monthly supplement of A&I (Anästhesiologie & Intensivmedizin). Thus they can be accessed and downloaded via www.ai-online.info. As being part of the journal, the recommendations will be quotable. Reprints can be ordered for payment.

A survey of until now in A&I published guidelines can be found on:

www.ai-online.info/Orphsuppl
www.orphananesthesia.eu

Projektleitung
Prof. Dr. Tino Münster, MHBA
Geschäftsführender Oberarzt
Facharzt für Anästhesie,
Spezielle Schmerztherapie,
Notfallmedizin
Anästhesiologische Klinik
Friedrich-Alexander-Universität
Erlangen-Nürnberg
Krankenhausstraße 12
91054 Erlangen, Deutschland
Tel.: 09131 8542441
Fax: 09131 8536147
E-Mail: muenster@kfa.imed.uni-erlangen.de

DGAI
Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin
www.dgai.de

A&I
ANÄSTHESIOLOGIE & INTENSIVMEDIZIN
www.ai-online.info

orphananesthesia

Anaesthesia recommendations for patients suffering from

Maple syrup urine disease

Disease name: Maple syrup urine disease

ICD 10: E71.0

Synonyms: MSUD, branched-chain ketoaciduria, branched-chain-alpha-ketoacid dehydrogenase deficiency, BCKD deficiency, BCKDH deficiency, ketoacid decarboxylase deficiency

Maple syrup urine disease (MSUD) is an autosomal recessive condition with an incidence of approximately 1 in 150,000 live births with a higher incidence amongst children from consanguineous relationships [1]. It is caused by an enzymatic deficiency with reduction in oxidative decarboxylation of branched-chain amino acids (BCAA) (leucine, isoleucine and valine) resulting in elevated levels and toxic metabolites that cause neurotoxicity [2].

The clinical features of MSUD are variable, but the "classic" form is characterised by psychomotor retardation, cerebral degeneration, hypoglycaemia, and seizures [3,4]. Adolescents with the condition may have attention-deficit hyperactivity disorder, anxiety, and developmental delay. The disease takes its name from the characteristic maple syrup odour of the urine from a metabolite of isoleucine [5]. Failure to thrive and feeding difficulties are also common.

Medicine in progress

Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

Disease summary

Presentation of the classic form occurs in the neonatal period, often with a metabolic ketoacidosis, due to accumulation of leucine and 2-oxo-isocaproate in the blood and tissues above critical concentrations during the first week of life [6]. If this is not identified and treated in a short time, the patient can die within a few days or weeks. Milder forms of the disease may present later in childhood.

The treatment of MSUD is two-staged, consisting of therapy to prevent acute decompensation and long-term nutrition therapy. Peritoneal dialysis has successfully reduced BCAA levels in neonates with MSUD [6]. The specific low protein diet limiting BCAA is a lifelong requirement, but compliance is not always optimal, and these children must be monitored carefully in order to prevent developmental delay and neurological decompensation. Adequate nutrition can be assured with the use of MSUD-specific medical foods (metabolic formulas) combined with low protein foods.

There are five clinical variants [2]:

1. Classic MSUD

The most common and severest form typically presents in the newborn period. There is little or no detectable branched-chain α-keto acid dehydrongenase complex activity (<2%) [7]. Patients are prone to decompensation, and neurological damage occurs if the condition is not treated.

2. Intermediate MSUD

Patients may become symptomatic at any age. There are variable features of neurological impairment and developmental delay. Decompensation can occur with catabolic illness, stress, inadequate caloric intake, or high protein consumption.

3. Intermittent MSUD

This is the second commonest variant where affected individuals appear completely normal and may have normal levels of the BCAA except during periods of extreme catabolic stress [7]. Symptoms usually present between 5 months and 2 years of age. Affected individuals are at risk of decompensation often presenting with ketoacidosis, and other typical features of neurotoxicity.

4. Thiamine-responsive MSUD

Some individuals with mild forms of MSUD have greater metabolic control when using supplemental thiamine. To date, there have not been individuals identified who can be successfully managed with thiamine alone without also limiting BCAA.

5. E3-deficient MSUD

This is a very rare form with only ten cases reported. Neonates are usually affected, with a lactic acidosis in addition to the typical presenting features. There is also an accumulation of both pyruvate and α-ketoglutarate in addition to the BCAA and their derivatives.

Decompensation

May be triggered by stressful situations such as injury or exercise, intercurrent illness, fasting, surgery, or caused by increased catabolism of endogenous protein.

The clinical manifestations are non-specific but include epigastric pain, vomiting, anorexia, muscle fatigue, and rarely pancreatitis. Neurological features may be similar to those of Wernicke encephalopathy including hyperactivity, lethargy, seizures, dystonia, hallucinations, and ataxia. If the condition is not treated, severe ketoacidosis with rapid neurological deterioration and hypoglycaemia can occur, proceeding to death secondary to cerebral oedema and herniation.

Typical surgery

Patients may present for all types of surgery, but day-case surgery should be avoided so that patients can be closely monitored post-operatively, and catabolism can be avoided.

Some patients with MSUD may be offered liver transplantation as part of the management of the disease.

Type of anaesthesia

The conduct of anaesthesia will depend upon the severity of symptoms. Both general and regional anaesthetic techniques are safe to use. Anaesthetic agents with anticonvulsant properties, such as propofol and thiopentone, have been used with no adverse effects, and some authors have also safely used ketamine [8,9]. Volatile anaesthetic agents and nitrous oxide are safe to use as are all muscle relaxants [5,6,8]. Short-acting agents, such as desflurane and remifentanil, may be preferred in order to facilitate recovery and minimise depressant effects on the respiratory system [6].

Effective pain management is essential, and therefore regional anaesthetic techniques should be considered as part of a multi-model approach to pain control. Local anaesthetic drugs are safe to use. Tramadol is also safe to use in patients with MSUD [8].

Necessary additional diagnostic procedures (preoperative)

General principles.

An assessment of the patients' clinical and biochemical status must be made pre-operatively. A baseline venous or arterial blood gas should be performed to ascertain the patients' metabolic state. If a severe acidosis is present, surgery should be delayed where possible until this can be corrected [6].

Careful fluid management is required pre-operatively aiming for normovolaemia. Prolonged fasting will cause dehydration and acidosis, whilst over hydration risks cerebral oedema [6,10]. Glucose containing fluids (e.g. 10% dextrose at 8 – 10 mg.kg-1.min-1) should be commenced at the start of the fasting period to avoid catabolism and resultant metabolic decompensation. Some authors have also advocated using an infusion of 20% intralipid pre-operatively, with specialist advice, in order to provide calories without causing over hydration and haemodilution [9].

Patients presenting with metabolic decompensation must be optimised prior to surgery [6].

Elective and emergency surgery.

For elective surgery, patients should be scheduled first on the operating list and ideally managed in a specialist centre with expertise in the management of MSUD. A multidisciplinary team approach is required during the perioperative period with intensive care facilities available in case of decompensation. The metabolic team should be involved in optimising the patient pre-operatively and provide advice during the perioperative period [10].

Elective surgery should be postponed if there is evidence of intercurrent illness that may increase the risk of decompensation.

Patients presenting for emergency surgery should ideally be transferred to specialist centres. If this is not possible, specialist metabolic advice should be sought. Good communication between the various members of the multidisciplinary team is essential.

Particular preparation for airway management

Standard management.

Particular preparation for transfusion or administration of blood products

Standard management.

Particular preparation for anticoagulation

Standard management.

Particular precautions for positioning, transport or mobilisation

Standard management.

Probable interaction between anaesthetic agents and patient's long-term medication

There have been no reported incidents of anaesthetic drug interactions and the patients' special dietary therapy.

Anaesthesiologic procedure

The patients' special diet and oral supplementation must be maintained perioperatively. A dextrose infusion should be continued to prevent hypoglycaemia and catabolism while the patient is fasting and throughout the procedure. This can be stopped when the patient resumes their normal diet. Early resumption of enteral intake is recommended, and as such anaesthetic techniques that facilitate recovery should be considered (e.g. postoperative nausea and vomiting prophylaxis; minimize opioid use by using regional techniques).

Invasive monitoring with an arterial line or central venous access is recommended for prolonged surgery where patients are at risk of metabolic acidosis to enable regular sampling for glucose levels and blood gas measurements.

Adequate tissue perfusion and avoidance of hypothermia are important to prevent metabolic acidosis. Temperature monitoring and intraoperative warming with fluid warmers and forced-air warming devices are recommended. If metabolic acidosis does develop, ensure the patient is adequately hydrated and consider administering an infusion of sodium bicarbonate.

Patients undergoing procedures that may cause blood to accumulate in the stomach, e.g. oral or gastrointestinal surgery, should have a nasogastric tube inserted as blood in the gastrointestinal tract represents a large protein load, and may trigger an acute decompensation [5,10].

Particular or additional monitoring

As described above, monitor blood glucose and venous or arterial blood gas measurements at regular perioperative intervals.

Possible complications

Metabolic decompensation.

Cerebral oedema.

Hypoglycaemia.

Postoperative care

Close monitoring of the patient's blood glucose, urinary ketones and plasma amino acid level is required until they resume their normal dietary intake.

Patients at high risk for metabolic or clinical deterioration must be cared for in a high dependency unit postoperatively. Regular monitoring of their acid-base status is needed to recognise decompensation early.

Information about emergency-like situations / Differential diagnostics

caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the disease

Management of metabolic decompensation.

It is important to reverse catabolism by providing adequate calories through the use of glucose (and possibly insulin), intralipids, and appropriate amino acid solutions. Intravenous fluid resuscitation promotes a diuresis to lower plasma leucine concentrations. Detoxification may also be achieved by removal of BCAA with peritoneal dialysis or haemodialysis [6].

Cerebral oedema secondary to hyponatraemia may develop, and this should be treated with hypertonic saline, mannitol or furosemide [2].

The use of hypertonic glucose solutions may, however, cause an additional stress factor with increases in oxygen consumption, carbon dioxide production, and release of noradrenaline. These patients may therefore benefit from fat emulsions that provide calorific intake without causing over hydration and haemodilution [6].

Ambulatory anaesthesia

In general, day-case surgery is not recommended, as the patient requires close monitoring postoperatively.

However, some specialist units with expertise in managing these patients may perform day-case procedures such as MRI scans under general anaesthesia or allow children with milder forms of MSUD to have day-case surgery.

Obstetrical anaesthesia

Successful management means more women are reaching child-bearing age, and there are a few case reports of successful pregnancies in patients with MSUD [11,14].

General principles of maintaining a high-calorie, low BCAA diet are recommended during labour or the perioperative period, and in some case parental nutrition has been used [11].

Tchan et al. discussed their management of two women with MSUD during their pregnancies [12]. They outline a detailed management plan for the peri-partum period for one of the patients that included six hourly blood glucose measurements, daily amino acid measurements, high energy supplements, infusion of dextrose containing fluids and intralipid 20% when not tolerating oral intake. Patients are at risk of decompensation post-partum due to the protein load from the involuting uterus. The management of labour pains was not referred to in these cases.

A good working labour epidural will ensure optimal analgesia during delivery, and potentially reduce the risk of acute decompensation occurring secondary to the stress response. Labour pains may also be successfully controlled with patient controlled intravenous opioid analgesia where regional anaesthesia is contraindicated.

Literature and internet links

1. Wilcken B. Maple syrup urine disease, www.orphan.net, accessed November 25th 2014
2. Bodamer O. Overview of maple syrup urine disease, www.uptodate.com, http://www.uptodate.com/contents/overview-of-maple-syrup-urine-disease, accessed September 30th 2014
3. Schwartz J, Kolendrianos E. Maple Syrup Urine Disease. A Review with a report of an additional case. Develop. Med. Child Neurol 1969;11:460-70
4. Levin M, Scheimann A, Lewis R, Beaudet A. Cerebral edema in maple syrup urine disease. J Pediatr 1993;122(1):167-8
5. Delaney A, Gal T. Hazards of anaesthesia and operation in maple-syrup-urine disease. Anesthesiology 1976;44(1):83-6
6. Kahraman S, Ercan M, Akkuş Ö, et al. Anaesthetic management in maple syrup urine disease. Anaesthesia 1996;5 :575-8
7. Axler O, Holmquist P. Intermittent maple syrup urine disease: two case reports. Pediatrics 2014;133(2):e458-60
8. Fuentes-Garcia D, Falcon-Arana L. Perioperative management of a patient with maple syrup urine disease. Br. J. Anaesth 2009;102(1):144-5
9. McCarron E, McCormack O, Howard C, et al. Management of maple syrup urine disease in the peri-operative period. Ir Med J 2013;106(9):277-8
10. Stuart G, Ahmad N. Perioperative care of children with inherited metabolic disorders. Continuing education in anaesthesia, Critical Care and Pain 2011:11(2):62-8
11. Wessel A, Mogensen K, Rohr F, et al. Management of a woman with maple syrup urine disease during pregnancy, delivery and lactation. J Parenter Enteral Nutr March 11th 2014, doi:10.1177/0148607114526451
12. Tchan M, Westbrook M, Wilcox G, et al. The management of pregnancy in maple syrup urine disease: experience with two patients. JMID Reports 2013:10:113-7
13. Van Calcar S, Harding C, Davidson S, et al. Case reports of successful pregnancy in women with maple syrup urine disease and propionic academia. Am J Med Genet 1992;44:64
14. Grünewald S, Hinrichs F, Wendel U. Pregnancy in a woman with maple syrup urine disease. J Inherit Metab Dis 1998;21:89.

Last date of modification: July 2015

These guidelines have been prepared by:

Author
Sian Griffith, Anaesthesiologist, Great Ormond St Hospital for Children, London, United Kingdom
sian.griffiths@doctors.org.uk

Co-Author
Grant Stuart, Anaesthesiologist, Great Ormond St Hospital for Children, London, United Kingdom
Grant.Stuart@gosh.nhs.uk

Peer revision 1
Mahmut Alp Karahan, Anaesthesiologist, Harran Üniversitesi Tıp Fakültesi, Ministry Health Suruç State Hospital, Şanlıurfa, Turkey
mahmutalp_k@yahoo.com

Peer revision 2
Dianne Frazier, Department of Paediatrics, University of North Carolina, Chapel Hill, USA
dianne_frazier@med.unc.edu

orphananesthesia
a project of the German Society of Anaesthesiology and Intensive Care Medicine
www.orphananesthesia.eu

Herausgeber

DGAI
Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V.
Präsidentin: Prof. Dr. Th. Koch, Dresden

BDA
Berufsverband Deutscher Anästhesisten e.V.
Präsident: Prof. Dr. G. Geldner, Ludwigsburg

DAAF
Deutsche Akademie für Anästhesiologische Fortbildung e.V.
Präsident: Prof. Dr. F. Wappler, Köln

Schriftleitung
Präsident/in der Herausgeberverbände

Gesamtschriftleiter:
Prof. Dr. Dr. Kai Zacharowski, Frankfurt

Stellvertretender Gesamtschriftleiter:
Prof. Dr. T. Volk, Homburg/Saar

CME-Schriftleiter:
Prof. Dr. H. A. Adams, Trier

Redaktionskomitee
Prof. Dr. G. Beck, Wiesbaden
Dr. iur. E. Biermann, Nürnberg
Prof. Dr. H. Bürkle, Freiburg
Prof. Dr. B. Ellger, Münster
Prof. Dr. K. Engelhard, Mainz
Prof. Dr. M. Fischer, Göppingen
Priv.-Doz. Dr. T. Iber, Baden-Baden
Prof. Dr. U. X. Kaisers, Ulm
Prof. Dr. W. Meissner, Jena
Prof. Dr. C. Nau, Lübeck
Dr. M. Rähmer, Mainz
Prof. Dr. A. Schleppers, Nürnberg
Prof. Dr. G. Theilmeier, Oldenburg
Prof. Dr. M. Thiel, Mannheim
Prof. Dr. F. Wappler, Köln
Prof. Dr. M. Weigand, Heidelberg

Redaktion
Alexandra Hisom M.A. &
Dipl.-Sozw. Holger Sorgatz

Korrespondenzadresse: Roritzerstraße 27 | 90419 Nürnberg | Deutschland
Tel.: 0911 9337812 | Fax: 0911 3938195
E-Mail: anaesth.intensivmed@dgai-ev.de

Verlag & Druckerei

Aktiv Druck & Verlag GmbH
An der Lohwiese 36 |
97500 Ebelsbach | Deutschland
www.aktiv-druck.de

Geschäftsführung
Wolfgang Schröder | Jan Schröder | Nadja Schwarz
Tel.: 09522 943560 | Fax: 09522 943567
E-Mail: info@aktiv-druck.de

Anzeigen | Vertrieb
Pia Engelhardt
Tel.: 09522 943570 | Fax: 09522 943577
E-Mail: anzeigen@aktiv-druck.de

Verlagsrepräsentanz
Rosi Braun
PF 13 02 26 | 64242 Darmstadt
Tel.: 06151 54660 | Fax: 06151 595617
E-Mail: rbraunwerb@aol.com

Herstellung | Gestaltung
Manfred Wuttke | Stefanie Triebert
Tel.: 09522 943571 | Fax: 09522 943577
E-Mail: ai@aktiv-druck.de

Titelbild
Dipl.-Designerin Monique Minde, Nürnberg

Erscheinungsweise 2016
Der 57. Jahrgang erscheint jeweils zum Monatsanfang, Heft 7/8 als Doppelausgabe.

Gemäß den Allgemeinen Geschäftsbedingungen, Punkt 3, tritt die Erhöhung für laufende und bereits bezahlte Abonnements zum 1. Januar 2017 in Kraft.

Die neuen **Bezugspreise** (inkl. Versandkosten) ergeben sich wie folgt:

- **Einzelhefte** 30,- €
- **Jahresabonnement:**
  Europa (ohne Schweiz) (inkl. 7 % MwSt.) 258,- €
  Schweiz 266,- €
  Rest der Welt 241,- €

  Mitarbeiter aus Pflege, Labor, Studenten und Auszubildende (bei Vorlage eines entsprechenden Nachweises)
  Europa (ohne Schweiz) (inkl. 7 % MwSt.) 94,- €
  Schweiz 90,- €
  Rest der Welt 94,- €

Für Mitglieder der DGAI und/oder des BDA ist der Bezug der Zeitschrift im Mitgliedsbeitrag enthalten.

Allgemeine Geschäfts- und Lieferbedingungen
Die allgemeinen Geschäfts- und Lieferbedingungen entnehmen Sie bitte dem Impressum auf www.ai-online.info

Indexed in **Current Contents®/Clinical Medicine, EMBASE/Excerpta Medica; Medical Documentation Service; Research Alert; Sci Search; SUBIS Current Awareness in Biomedicine; VINITI: Russian Academy of Science.**

Wichtiger Hinweis
Für Angaben über Dosierungsanweisungen und Applikationsformen kann vom Verlag und den Herausgebern keine Gewähr übernommen werden. Derartige Angaben müssen vom jeweiligen Anwender im Einzelfall anhand anderer Literaturstellen auf ihre Richtigkeit überprüft werden. Gleiches gilt für berufs- und verbandspolitische Stellungnahmen und Empfehlungen.

Zugangsdaten für **www.ai-online.info** können Sie unter Angabe Ihrer Mitglieds- oder Abonummer anfordern unter der E-Mail-Adresse: **ai@aktiv-druck.de**

CONTACT US

Please do not hesitate to contact us. We will be glad to answer and provide further information to you at any time.

....
Name

....
First Name

....
Department / Hospital

....
Place

....
Telephone

....
E-Mail

....
Date / Signature

Please contact me for further information ◯

I would like to participate in the project ◯

ADDRESS

German Society of Anaesthesiology and
Intensive Care Medicine
Nina Schnabel
Roritzerstrasse 27 I 90419 Nuremberg I Germany
Tel.: +49-911-9337822 | Fax: +49-911-3938195
Email: nschnabel@orphananesthesia.eu