Received October 2012, accepted October 2012

HOT TOPICS

Summary of hot topics session, European Society of Intensive Care Medicine

17 October 2012, Lisbon, Portugal

Dr M van der Jagt

Department of Intensive Care, Erasmus MC – University Medical Center Rotterdam

Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control

Mesotten D, et al. JAMA 2012:24;308(16):1641-50.

Background. In a previous study in paediatric critically ill patients, tight glucose control (TGC) improved acute mortality but there was concern about cognitive outcomes because of a major increase in the rate of hypoglycemia in the treatment arm (defined as a glucose<2.2 mmol/L, 24.9% versus 1.4% in standard care group).

Objective. To assess intelligence 4 years after randomisation to the TGC study.

Patients and Methods. All 700 children included in the previous RCT were approached for follow up. For comparison, 216 matched healthy children (102 siblings).

Main results. IQ 88.5 controls and 88.0 in TGC group versus 103 in matched healthy children (P=0.70). For more complex intellectual tasks, the children in the TGC group tended to have better outcomes, approaching those in the healthy controls. Subanalysis of children with hypoglycemia in TGC versus usual care group confirmed the absence of adverse cognitive consequences of TGC.

Clinical implications. Hypoglycemia during TGC in critically ill children, in spite of a 25% incidence, did not affect cognitive outcome in survivors, and even improved motor coordination and cognitive flexibility. It is argued that hyperglycemia may be more deleterious to the developing brain than brief hypoglycemia.

Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol. A randomized controlled trial. SLEAP investigators, and the Canadian Critical Care Trials Group.

Mehta S, et al. JAMA 2012;308(19):doi:10.1001/jama.2012.13872

Background. Minimisation of sedation in critically ill patients improves outcome. However, concerns exist about daily sedation interruption with regard to patient discomfort, device removal, and clinician workload.

Objective. To assess whether critically ill patients who were managed according to a nurse-driven analgesia/sedation (opioids and benzodiazepines only) protocol would benefit from daily interruption of analgesia/sedation.

Patients and Methods. Multicenter randomized controlled clinical trial (Canada/US) in adult patients anticipated to be mechanically ventilated ≥ 48 hours. Patients after cardiac arrest, with traumatic brain injury, those receiving neuromuscular blocking agents, with limitation of life support and with no informed consent were excluded. Primary outcome was the duration of mechanical ventilation from intubation to extubation, or tracheostomy mask for at least 48 h. The sedation goal in both groups was light sedation (comfortable and arousable) with an intent to wean sedation to zero when feasible. A weaning protocol including daily screen for unassisted breathing was used. Daily interruption of sedation was done in the intervention group.

Main results. More than 80% had a medical as opposed to surgical or traumatic condition (N=423). There were no differences in the primary outcomes between the two treatment groups. Patients in the intervention group received 102 mg of midazolam equivalent/day versus 82 mg in the control group (P=0.04) and 1780 mcg of fentanyl equivalent/day versus 1070 mcg (P<0.0001). Hospital mortality was similar in both groups (30%). Nurses found the workload higher in the intervention group.

Clinical implications. For critically ill mechanically ventilated patients managed according to a nurse-driven protocol aimed at light sedation, daily interruption of sedation did not reduce duration of mechanical ventilation.

The PROSEVA trial: Effect of prone positioning in patients with severe and persistent acute respiratory distress syndrome.

Guerin C, et al. Submitted.

Background. There is still uncertainty about the effect of prone positioning in acute respiratory distress syndrome (ARDS) on mortality.

Objective. To demonstrate that prone position (PP) can reduce mortality in patients with severe and persistent ARDS.

Patients and Methods. This trial included adult patients, intubated for <36 h, with ARDS according to the consensus criteria, which had to be confirmed 12-24 h later, and with the following criteria present: PaO2/FiO2 (PF) ratio<150, FiO2>0.6, PEEP≥5 cmH2O and tidal volume (Vt) of 6ml/kg ideal body weight. Exclusion criteria were increased intracranial pressure, massive hemoptysis, tracheal surgery, facial trauma, deep venous thrombosis, unstable bone fractures, mean arterial pressure<65 mmHg, pregnancy, chest tube with air leak, inhaled nitric oxygen, extracorporeal membrane oxygenation, lung transplant, non-invasive ventilation>24 h. PP

Correspondence

M. van der Jagt

E-mail: m.vanderjagt@erasmusmc.nl

had to be instituted for at least 16 h or until stopping rules including lower mechanical ventilatory support, serious complications during PP or PF ratio decrease>20%. Targets in both groups were pH>7.20, Vt 6ml/kg, plateau pressure≤30 cmH2O, SpO2≥88%. Sedation interruption and subsequent weaning were tried when in supine position PEEP was <10 cmH2O, PF ratio>150 and FiO2<0.6.

Main results. Baseline characteristics (N=466) were similar except for a lower Sequential Organ Failure Assessment (SOFA) score (10.4 vs 9.6, P=0.01) in the control group. Most patients had a primary ARDS due to pneumonia and aspiration. At inclusion both groups had a mean PEEP of 10 cmH2O with FiO2 0.8, pH 7.30, plateau pressure 24 cmH2O, lactate between 2 and 3. Mortality was 33% in the SP versus 16% in the PP group (P<0.0001), with a hazard ratio after adjustment for SOFA of 0.42 (0.26-0.66) at 28 days. More patients had a cardiac arrest in the SP group (13.5%, versus 6.4%).

Clinical implications. Prone positioning in severe and persistent ARDS in patients that fitted the inclusion criteria in this trial reduced mortality significantly. Baseline mortality seems lower than in previous trials. Reasons given by the presenting author for the large treatment effect found in this trial may include: long PP sessions, stopping rules for PP, lower PEEP (less hemodynamic worsening).

Albumin for volume replacement in severe sepsis. The ALBIOS trial, preliminary results.

Gattinoni L, et al. To be submitted

Background. Possible benefit of albumin on mortality was found in the SAFE study in septic patients.

Objective. Does resuscitation with albumin improve survival at 28 and 90 days in severe sepsis and septic shock compared with crystalloids.

Patients and Methods. Patients with severe sepsis and septic shock were included after a period of initial early goal directed therapy according to the Rivers protocol. Patients were randomised for crystalloids alone versus albumin and crystalloids as fluid for resuscitation targeted at >30g/L plasma albumin, both in the acute phase according to early goal directed therapy and until day 28. No other colloids were allowed during this period.

Main results. N=1815. Mortality was 35% in both groups at discharge. There was a trend towards less mortality in patients with severe septic shock.

Clinical implications. To be determined after publication of final results.

C.H.E.S.T.: Crystalloids Hydroxy-Ethyl Starch Trial.

Myburgh JA, et al. N Engl J Med 2012 Oct 17. [Epub ahead of print]

Background. Hydroxy-ethyl starches (HES) are widely used but there is concern with regard to risk of kidney injury and potential adverse effect on outcome in critical illness.

Objective. To assess safety and efficacy of 6% hydroxy-ethyl starch (130/0.4) as compared with 0.9% sodium chloride alone for fluid resuscitation in adult patients treated in the ICU.

Patients and Methods. Multicenter randomized controlled clinical trial across New Zealand and Australia. Patients received up to 50ml/kg of study fluid per day in accordance with maximum hydroxy-ethyl starch dose, followed by open-label 0.9% saline. Intervention was fluid resuscitation to correct hypovolemia at any time during ICU treatment according to the treating physician, and supported by one or more predefined criteria for hypovolemia. Patients with intracranial hemorrhage, dialysis dependent renal failure, burns, cardiac surgery, or liver transplant patients were excluded.

Main results. Relative risk for mortality was 1.06 in the HES group vs controls (NS, P=0.26, mortality 18% versus 17%). RR was 1.21 (P=0.04) for use of renal replacement therapy in the HES group (7.0% versus 5.8%). Pruritus and skin reactions were more prevalent in the HES group.

Clinical implications. The use of 6% HES (130/0.4) did not improve mortality as compared with normal saline for resuscitation in ICU patients, but was associated with a higher risk for RRT. HES did not confer any benefit in any subgroup over normal saline.

EuSOS: European Surgical Outcomes Study.

Pearse R, et al. Lancet. 2012 Sep 22;380(9847):1059-65.

Background. Surgical outcome data are generally of poor quality and not comparative across Europe.

Objective. To assess in hospital mortality across a wide range of surgical patients, and hospital and critical care stay in 28 European nations.

Patients and Methods. Observational 7 day cohort study with follow up until hospital discharge. All adult patients undergoing in-patient non-cardiac surgery during a 7 day period (April 2011) were included. Obstetric, neurosurgery and cardiac surgery patients were excluded.

Main results. Mortality rates after surgery were higher than expected from previous data (N=46 539, overall mortality 4%, range 1.2% for Iceland to 21.5% for Latvia). Evidence was found of international variation in mortality and critical care allocation to this population.

Clinical implications. Variations in mortality between countries suggest the need for national and international strategies to improve care for these patients.

Received September 2011; accepted March 2012

CASE REPORT

GHB withdrawal syndrome: a possible life threatening condition

L van Koppenhagen, AJ Paling

Department of Intensive Care Medicine, Jeroen Bosch Hospital, 's Hertogenbosch

Abstract - Chronic use of gamma-hydroxybutyrate (GHB) can cause dependency. Subsequent acute cessation may lead to a variety of withdrawal symptoms. We present the case of a 22-year old man with a life-threatening GHB withdrawal syndrome, including delirium, autonomic dysfunction, rhabdomyolysis and renal failure. As high dosages of sedatives were ineffective, medical GHB was added to the treatment regimen. After 19 days of ICU treatment, he fully recovered. This case report describes the pathophysiology of the GHB withdrawal syndrome and discusses the options for treatment.

Keywords - **Gamma-hydroxybutyrate, withdrawal, rhabdomyolysis, renal failure, treatment, medical GHB**

Introduction

Gamma-hydroxybutyrate (GHB), an analogue of gamma aminobutyric acid (GABA), was originally synthesized as an anaesthetic. Due to associated side effects, its clinical use is currently limited to the treatment of narcolepsy and alcoholism. GHB is increasingly popular as a party drug for its euphoric and aphrodisiac effects, and is notorious as a 'rape drug'. Overdose occurs frequently in occasional users, but recovery is usually rapid and uneventful. Chronic use of GHB can cause severe dependence, and withdrawal symptoms may occur within hours after abrupt cessation [1]. In this case report, we describe the case of a patient with a life-threatening withdrawal syndrome after discontinuing chronic GHB use and we discuss the options for treatment.

Case report

A 22-year-old male had been using an increasing amount of GHB for two years, resulting in daily use of up to a litre and a half of self-made GHB of unknown concentration around-the-clock. He abruptly stopped taking GHB because he ran out of money. Within a couple of hours, he developed tremor, agitation, hallucinations and seizures. He was taken to the emergency department of another hospital and subsequently admitted to the emergency ward of a psychiatric hospital. Diazepam 10 mg orally 6 times daily was prescribed. Over the next few days, he was hypertensive, tachycardic, extremely agitated and suffering from severe hallucinations. Because of fever, laboratory abnormalities and ongoing delirium despite administration of several sedative agents (diazepam, haldol, cisordinol and GHB), he was transferred to the emergency department of our hospital on day three.

On arrival, we saw a confused, agitated and extremely combative man, who had to be restrained by a number of people. He was covered with bruises, crusts and scratch marks. Vital signs showed a heart rate of 120 bpm, blood pressure 125/75 mmHg, body temperature 37.8 ^{0}C, oxygen saturation 93% on room air. Laboratory results revealed elevated levels of serum creatinine 443 mmol/L, urea 29.4 mmol/L, creatine kinase (CK) 198798 U/L, aspartate aminotransferase (AST) 1688 U/L, alanine aminotransferase (ALT) 571 U/L, lactate dehydrogenase (LD) 5294 U/L. Urine drug screen was not performed, as he had already been hospitalised for three days. Ultrasonography of his kidneys and liver showed no abnormalities.

Repeated doses of midazolam i.v. did not yield any effect on the agitation or combativeness. To prevent any further deterioration, the patient was transferred to the intensive care unit (ICU) for sedation, tracheal intubation and mechanical ventilation. Infusion with a combination of normal saline and sodium bicarbonate was initiated for renal failure and severe rhabdomyolysis. His urinary output was 50 ml h^{-1}. Renal replacement therapy was not initiated.

Despite a combination of multiple sedative agents in high dosages (midazolam 25 mg h^{-1}, propofol 300 mg h^{-1}, remifentanil 8 ug kg^{-1} h^{-1}, clonidine 0.4 mg h^{-1} and haldol 3mg i.v. t.i.d.), the patient remained agitated and combative. After consultation of an expert in the treatment of GHB-withdrawal syndromes, we added medical GHB (Xyrem®), 1 gram 12 times daily to the treatment regime. After one week of ICU-treatment, self-extubation occurred. Because of ongoing extreme agitation accompanied with desaturations after lowering his sedatives, a percutaneous dilatation tracheostomy was performed.

In the following week, we could very slowly diminish the amount of sedatives. The GHB was gradually tapered to zero in twelve days. Renal function and serum CK, AST, ALT and LD normalised. On day 16, the patient was weaned from mechanical ventilation and the tracheostomy tube was removed. 19 days after admission, he was transferred to a psychiatric hospital for further treatment of his GHB dependence.

Correspondence

L van Koppenhagen

E-mail: lvankoppenhagen@gmail.com

Discussion

The most important clinical effect of exogenous GHB administration is inhibition of the central nervous system by mechanisms mediated by binding of GHB to the γ-aminobutyric acid (GABA)$_B$ receptor [1]. Chronic use of GHB can lead to tolerance due to down-regulation of GABA-receptors [2,3]. Subsequent withdrawal of GHB results in a boost of excitatory neurotransmitters as a result of decreased GABA-inhibition [2]. The withdrawal syndrome that follows often starts with mild symptoms like tremor, diaphoresis, restlessness, insomnia, nausea, vomiting and anxiety. After hours to days, this may progress to severe withdrawal syndrome with refractory agitation, hallucinations, tachycardia, hypertension, hyperthermia and delirium [1,2,4]. Rhabdomyolysis, seizures and death have been reported [2,3,5]. This case is one of the most severe cases of GHB withdrawal syndrome described in the literature. It is unique in the severity of the rhabdomyolysis and is one of the first reported cases of renal failure as part of the GHB withdrawal syndrome [6]. Despite the seriousness of the renal failure and rhabdomyolysis, we did not find hyperkalemia in this patient. Because of a steady urinary output on high fluid infusions and the absence of hyperkalemia, renal replacement therapy was not initiated.

Although the use and abuse of GHB have grown over the years, treatment of the withdrawal syndrome has not yet adequately been investigated and protocols are lacking [7]. Benzodiazepines, alone or in combination with other drugs, are frequently mentioned as agents of first choice, but are often ineffective [1-4,,8,9]. Benzodiazepines are indirect $GABA_A$ agonists, acting by increasing the receptor affinity for GABA, rather than by directly stimulating the receptor. They are thus less effective when central GABA stores are depleted or when receptors are down regulated [4]. Furthermore, benzodiazepines bind the $GABA_A$ receptor, whereas GHB mainly binds the $GABA_B$ receptor [5,7]. This might explain the extremely high dosages often required to control the withdrawal state.

Although considered ineffective and carrying the risk of substantial side effects such as dystonia and lowering the seizure threshold, antipsychotics are used regularly in the treatment of this withdrawal syndrome [4,8,10]. Some other treatments, such as pentobarbital or baclofen, have been suggested for benzodiazepine-resistant cases [4,5,11]. Based on the pharmacologic profile, treatment with the $GABA_B$ agonist baclofen seems argumentative [8]. However, only a few reports of one treatment with baclofen have been published so far [3,5]. Low dose baclofen (5 to 10 mg t.i.d.) has successfully been used in a patient with seizures as part of the GHB withdrawal syndrome [5]. Considering the lack of experience, we think baclofen should only be used when other options fail.

Currently, clinical detoxification with medical GHB in a gradually tapering dosage is being investigated in the Netherlands [12]. The results of a pilot study have recently been published. Twenty-three consecutive patients were transferred from illegal GHB to pharmaceutical GHB. After a titration period, they were placed on a 1-week taper. The results are promising: despite of the large amount of GHB the patients used to take, only mild withdrawal symptoms were reported. None of the patients had to be transferred to a medium or intensive care unit [6]. This pilot study has resulted in a *practice-based recommendation* which was presented at a conference for professionals in addiction medicine in December 2011. The proposed treatment protocol consists of two phases. During the first phase, the titration phase, the patient is stabilized on medical GHB. The starting dose is 60 to 70% of the self-administered dose. Every two hours, adjustment of the dose takes place based on the observed withdrawal symptoms. Due to the large variations in the amount of GHB patients are used to taking, the administered amount of medical GHB may vary from patient to patient. After the patient has been stabilized on medical GHB, the second phase, or detoxification phase, of gradually tapering the GHB follows. The GHB is administered every three hours and the dose is subsequently lowered to zero with 2-3 ml per gift per day (based on GHB with a concentration of 150 mg/ml) [13].

Treatment with medical GHB has also been proposed for cases refractory to other sedative agents [14]. When our patient was admitted, the previously mentioned pilot study was running [6]. The first results seemed positive which was the reason why we started treatment with medical GHB instead of a different none-evidence based treatment such as baclofen. In our case, adding medical GHB to the treatment regimen did not resolve the withdrawal symptoms and we still needed high dosages of other sedatives, but adding GHB did help in creating a manageable situation. Retrospectively, higher dosages of medical GHB might have been required considering the large amount of GHB the patient used to take.

In our opinion, detoxification and treatment of withdrawal symptoms with medical GHB deserve further investigation. Controlled prospective studies are necessary to develop and evaluate treatment protocols for this possible life-threatening condition.

We would like to thank Rama Kamal for her commentary on the manuscript.

References

1. Snead OC 3rd, Gibson KM. Gamma-hydroxybutyric Acid. N Engl J Med 2005;352:2721-32.
2. Dyer JE, Roth B, Hyma BA. Gamma-Hydroxybutyrate Withdrawal Syndrome. Ann Emerg Med 2001;37:147-53.
3. Wojtowicz JM, Yarema MC, Wax PM. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. CJEM 2008;10:69-74.
4. McDonough M, Kennedy N, Glasper A, Bearn J. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. Drug Alcohol Depend. 2004;75:3-9.
5. LeTourneau JL, Hagg DS, Smith SM. Baclofen and Gamma-Hydroxybutyrate Withdrawal. Neurocrit Care 2008;8:430-3.
6. De Jong CA, Kamal R, Dijkstra BA, De Haan HA. Gamma-hydroxybutyrate detoxification by titration and tapering. Eur Addict Res 2012;18:40-5. Epub 2011 Dec 3.
7. Van Noorden MS, Kamal R, De Jong CAJ, Vergouwen AC, Zitman FG. GHB-afhankelijkheid en -onthoudingssyndroom: diagnostiek en behandeling. Ned Tijdschr Geneeskd 2010;154:A1286
8. Van Noorden MS, Van Dongen LC, Zitman FG, Vergouwen TA. Gamma-hydroxybutyrate withdrawal syndrome: dangerous but not well-known. Gen Hosp Psychiatry 2009;31:394-6.
9. Stijnenbosch PJ, Zuketto C, Beijaert PJ, Maat A. Onthoudingsdelier na het gebruik van GHB. Ned Tijdschr Geneeskd 2010;154:A1086.
10. Rosenberg MH, Deerfiels LJ, Baruch EM. Two cases of severe gamma-hydroxybutyrate withdrawal delirium on a psychiatric unit: recommendations for management. Am J Drug Alcohol Abuse 2003;29:487-96.
11. Sivilotti ML, Burns MJ, Aaron CK, Greenberg MJ. Pentobarbital for severe gamma-butyrolactone withdrawal. Ann Emerg Med 2001;38:660-5
12. Kamal R, Van Hoek AFM, de Haan HA, De Jong CAJ. Stoppen met gammahydroxybutyric acid (GHB), hoe doe je dat? In: De Jong CAJ, Van De Wetering BJM, De Haan HA (eds). Verslavingsgeneeskunde: Psychofarmacologie, psychiatrie en somatiek. Assen, Van Gorcum, 2009, pp 39-47.
13. Van Noorden M, Kamal R, Paling A, Hübner B. Behandeling van (acute) GHB-onthouding in het algemene ziekenhuis. Practice-based aanbeveling. Conceptversie gepresenteerd tijdens 'GHB-monitor', Nijmegen, 16-12-2011.
14. Veerman SR, Dijkstra HN, Liefting-Kluft I. Levensbedreigende onthoudingsverschijnselen door gammahydroxyboterzuur. Tijdschr Psychiatr 2010;52:411-6.