Molecular Adsorbent Recycling System Therapy in the Treatment of Acute Valproic Acid Intoxication

Sarah Dichtwald MD, Esther Dahan MD, Nimrod Adi MD, Avia Moses MD and Patrick Sorkine MD

Intensive Care Unit, Sourasky Tel Aviv Medical Center, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

KEY WORDS: MARS (molecular adsorbent recycling system), valproic acid intoxication, hyperammonemia, hemofiltration, hemodialysis

IMAJ 2010; 12: 307–308

Acute valproic acid intoxication may be a life-threatening condition, with involvement of multiple organ systems, including the liver, kidneys, brain, heart and bone marrow. We report a case of acute valproic acid intoxication in a young man presenting with hyperammonemia and encephalopathy. MARS therapy was initiated successfully with a decrease in ammonia and valproic acid levels and resolution of the encephalopathy.

PATIENT DESCRIPTION

A 29 year old man was admitted to the emergency room due to acute overdose of valproic acid. His medical history included alcohol abuse, anxiety and depression. He was medicated with escitalopram, clonazepam and valproic acid. Several hours prior to admission he ingested 10 g of valproic acid, and was brought to the ER while suffering from abdominal pain, nausea and drowsiness. In the ER he was treated with active charcoal and fluid resuscitation. He did not require respiratory support. His blood valproic acid level at admission was 236 µg/ml (therapeutic serum concentrations range from 50 to 125 µg/ml).

He was admitted to the intensive care unit where he was treated with fluids, active charcoal and thiamine. During hospitalization he was still confused and lethargic but required neither airway protection nor respiratory or inotropic support. Blood tests showed normal liver enzyme levels and coagulation; renal function tests were also normal, as were hemoglobin, glucose, electrolytes and platelets. His blood ammonia level was 400 µg/ml on admission (normal blood ammonia level 20–85 µg/dl). An arterial blood sample demonstrated a pH of 7.34; oxygenation and ventilation were adequate, lactate level was 4.6, his anion gap was 15 and his base excess minus 4.5.

Lactulose and carnitine, 50 mg/kg, were added to his therapeutic regimen and a course of molecular adsorbent recycling system was implemented. The rationale for using MARS in our patient was that since valproic acid has a high affinity to albumin, MARS, as an albumin-based dialysis, competing with the patient's endogenous albumin for valproic acid binding, can be used in the detoxification process.

During his stay in the ICU he regained full consciousness, his blood ammonia levels dropped to 278 µg/ml on the second day and to 157 and 50 µg/ml in the following days. He was released in satisfactory condition to the internal medicine department for further observation.

COMMENT

Extracorporeal removal of valproic acid by hemodialysis and hemofiltration in acute valproic acid intoxication has been reported in the literature [1,2]. Theoretically, the relatively low molecular weight and low volume of distribution of valproic enables potential benefit from extracorporeal therapy, but the high degree of protein binding of valproic acid hinders the efficiency of this method. However, at toxic high plasma levels of valproic acid, the protein binding sites become saturated and the efficiency of extracorporeal removal of valproate increases.

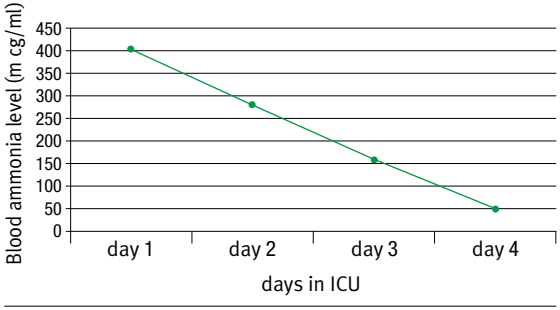
The use of a charcoal hemoperfusion cartridge may slightly increase the clearance of the drug, because there is direct contact of blood with an adsorbent that can remove even highly protein-bound drugs [3]. Hemodialysis may reverse the adverse metabolic effects of valproic acid intoxication.

To the best of our knowledge, this is the first report of MARS therapy for the treatment of acute valproic acid intoxication. MARS is an extracorporeal liver support device, usually used to provide time for hepatic regeneration or for donor availability for liver transplantation (bridge to transplantation) [4]. The principle underlying the extracorporeal liver support system is albumin dialysis, first introduced by Stange et al. [5]. This system mimics the biological feature of the hepatocyte membrane by transferring protein-bound and water-soluble toxic endogenous metabolites (such as ammonia, lactate and phenols) from the blood into a dialysate compartment through a special membrane [4]. The membrane in MARS is a highly permeable hollow fiber embedded with albumin and is used to dialyze the patient's blood against a dial-

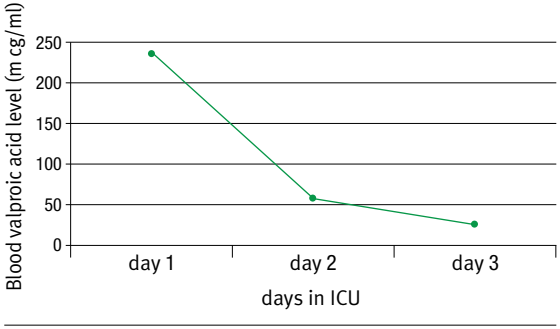
ER = emergency room

MARS = molecular adsorbent recycling system
ICU = intensive care unit

[A] Blood ammonia level during hospitalization



[B] Blood valproic acid level during hospitalization



ysis solution that contains toxin-binding carrier proteins [4].

The rationale for using MARS in our patient was that valproic acid has a high affinity to albumin, and therefore MARS can be used in the detoxification process.

Our patient did not present any signs of hepatic failure, and his encephalopathy and hyperammonemia were probably induced by the valproic acid intoxication and not by a secondary insult to the liver caused by the drug. Valproic acid may cause hyperammonemia by several mechanisms not hepatically related, which may explain the absence of elevated liver enzymes and normal coagulation factors in the presence of marked hyperammonemia. Nevertheless, the clearance of ammonia was facilitated by MARS therapy and the valproic acid levels in the patient's blood were markedly decreased once MARS therapy was initiated [Figure A].

The patient's valproic acid blood level was 236 μg/ml on admission and dropped to 59 μg/ml the following day. Two hours later the drug level was 27 μg/ml. Since the half-life of valproic acid is 7–15 hours, it is expected that when the drug level is 236 μg/ml, the elimination toward a therapeutic level will occur within 2 days. With MARS therapy, elimination of valproic acid seemed to be faster, with valproic acid levels dropping to the therapeutic range within 24 hours [Figure B]. Marked clinical improvement was demonstrated soon after MARS therapy, with the patient regaining full consciousness. This improvement may be attributed not only to valproic acid elimination via MARS therapy, but also to elimination of ammonia.

The standard care for patients with valproic acid overdose, when there is no overt liver damage or renal failure, is to observe the patient in an ICU setting. However, this patient was treated more aggressively, since despite supportive treatment consisting of fluids, active charcoal, lactulose and carnitine, no clinical improvement was noted.

In conclusion, we report the successful use of MARS therapy in a patient with acute valproic acid intoxication, hyperammonemia and encephalopathy. Further investigation is required to evaluate the benefits of MARS therapy in acute valproic acid intoxication compared to other hemodialysis and hemofiltration techniques.

Correspondence:
Dr. P. Sorkine
Intensive Care Unit, Sourasky Tel Aviv Medical Center, 6 Weizmann Street, Tel Aviv 64239, Israel
Phone: (972-3) 697-3247
email: sorkine@tasmc.health.gov.il

References

1. Van Keulen JGV, Gemke RJ, Van Wijk JAE, Touw DJ. Treatment of valproic acid overdose with continuous arteriovenous hemofiltration [Abstract]. *J Toxicol Clin Toxicol* 2000; 38: 219.
2. Hicks LK, McFarlane PA. Valproic acid overdose and haemodialysis. *Nephrol Dial Transplant* 2001; 16: 1483-6.
3. Kandrotas RJ, Love MJ, Gal P, Oles KS. The effect of hemodialysis and hemoperfusion on serum valproic acid concentration. *Neurology* 1990; 40: 1456-8.
4. Stange J, Mitzner SR, Risler T, et al. Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. *Artif Organs* 1999; 23: 319-30.
5. Stange J, Mitzner S. A carrier mediated transport of toxins in a hybrid membrane. Safety barrier between a patient's blood and a bioartificial liver. *Int J Artif Organs* 1996; 19: 677-91.