Case Report

Acute Valproic Acid Overdose: Enhance Elimination with Multiple-Doses Activated Charcoal

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Multiple dose activated charcoal (MDAC) is used to enhance elimination of toxic substance in acute poisoning. However, its role in acute valproic acid (VA) overdose is controversial. The authors report a case of VA overdose that successfully recovered with MDAC treatment. The half-life of VA in the presented patient was decreased from 12 to 8 hours during MDAC administration. MDAC treatment in acute poisoning enhanced VA elimination four times than without treatment. MDAC should be considered for the treatment of acute VA intoxication.

Keywords: *Valproic acid, Toxicity, Multiple dose activated charcoal, Hemodialysis*

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Valproic acid (VA), a standard anticonvulsant since 1978, is widely prescribed for bipolar disorder, schizophrenia and migraine prophylaxis. VA enhances levels of neurotransmitter at GABA receptor and prolongs the recovery of inactivated sodium channels. VA mainly metabolized by UDP-glucuronosyl transferase in liver. Patients with VA overdose present with gastrointestinal disturbance, variable CNS symptoms such as confusion, ataxia, tremor and coma. In severe cases, some patients may have cardio-vascular and respiratory arrest. Unfortunately, the incidence of VA overdose is increasing in parallel with the rise of its usage. Although the standard therapy for VA overdose is hemodialysis, enhancing elimination management may a therapeutic option[1]. Here, the authors report a case of VA toxicity treated with multiple dose activated charcoal (MDAC) to enhance the drug elimination.

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Case Report

A 24-year-old, Thai woman with a history of complex partial seizure was brought to a district hospital after taking 25.6 g of VA (200 mg/tablet) an hour before. On admission, the patient was confused and drowsy. She was treated by gastric lavage, activated charcoal and intravenous fluid. Seven hours later, the patient was referred to our tertiary care hospital, for hemodialysis. Her conscious state was unchanged, but she was hemodynamically stable with heart rate 94 beats per minute, a respiratory rate 22 times per minute, blood pressure 107/55 mmHg. Her Glasgow Coma Score (GCS) was 11/15. Other neurological examinations were in normal limits. Her serum electrolytes were as follows: sodium 147 mEq /L; potassium 3.6 mEq /L; chloride 114 mEq /L; and, CO_2 14.7 mEq /L. Metabolic acidosis was corrected by fluid replacement and sodium bicarbonate administration. On the admission, her VA blood level was 848.22 mg/mL (the therapeutic range of 50-100 mg/mL). The authors decided to use MDAC (activated charcoal 20 g NG every 4 hr) to enhance the elimination of VA. GCS was improved from 11/15 to 15/15 after 5 hours of MDAC are administration, hemodialysis was not considered.

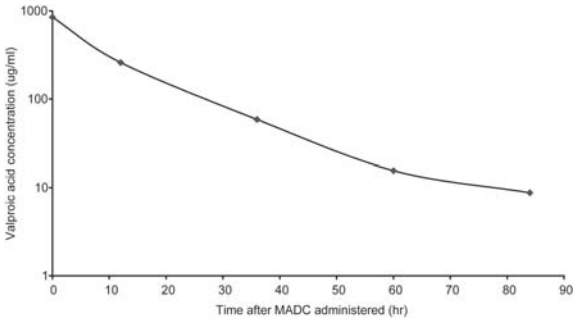

Fig. 1 Valproic acid concentration time curve after MDAC administration in our patient

After 12, 36, 60 and 84 hours of MDAC treatment, the patient's VA blood level decreased to 259.14, 58.38, 15.54 and 8.76 g/mL, respectively (Fig. 1).

Discussion

General management in VA overdose is decreased absorption by gastric lavage and single dose activated charcoal. In usual therapeutic cases, VA volume distribution is 0.2-0.3 L/kg and plasma protein binding between 90 and 95%[1]. Therefore, increased elimination by hemodialysis and MDAC seem ineffective because of high volume distribution and high protein binding. However, VA fraction unbound could be increased due to saturation of protein binding during acute overdose. Recent data showed plasma protein binding decreased to 35% when plasma level was in toxic levels of (300 ug/ml). Therefore, MADC and hemodialysis may be useful to increase elimination in VA toxicity. Hicks LK et al showed that VA half-life decreased from 31.3 hours at pre-dialysis to 2.5 hours during 7.7 hours hemodialysis. The patient regained consciousness after hemodialysis. In another successful case report, VA half-life was decreased from 7.2 hours to 2.4 hours during 6 hours of hemodialysis[3]. Clinical improvement was 5 hours after hemodialysis started. Although hemodialysis can enhance elimination half-life more effectively than MDAC, it is only indicated in coma patients with hemodynamically-unstable, severe metabolic acidosis that cannot be corrected by fluid replacement, and plasma levels higher than 1000 g/mL[4]. MDAC use is still controversial for the increase of elimination in VA toxicity patients. It was found VA half-life was not statistically different between control and treatment groups with MDAC (20 $\pm$ 6.8 hours and 22 $\pm$ 9.2 hours) after administration of VA 300 mg[5] However, that study[5] was conducted in healthy volunteers by whom the condition was different to VA overdose with saturation of protein binding and saturation of metabolism. As the result, MDAC would not diminish the plasma half-life in this study. On the other hand, Farrar HC reported the case of a patient who ingested 4.5 g VA and had been treated with MDAC. VA half-life decreased to 4.8 hours during MDAC treatment. Twenty-four hours later, VA levels diminished from 815 to 56 mg/mL[6].

For the presented case, the patient was drowsy and hemodynamically stable, therefore hemodialysis might be unnecessary. Twelve hours after the MDAC dosing, serum VA concentration decreased from 848.22 to 259.14 mg/mL. Half-life of VA in the presented patient was decreased to 8 hours during MDAC administration. Therefore, MDAC treatment had enhanced elimination by four times than acute poisoning without this treatment. MDAC not only increased elimination of VA in the presented patient but also clinical improvement was observed. Although hemodialysis increases VA elimination three times more than MDAC, the latter is more available to primary hospitals. Moreover, MDAC is not difficult to administer with less complication. On the other hand, the hemodialysis procedure is more complicated and usually needs tertiary care and takes time to perform. However, there are no data for the combined treatment between hemodialysis and MDAC.

Conculsion

The authors conclude that MDAC is beneficial to enhance elimination in acute VA intoxication and should be considered in any primary hospital to bring about better outcome for its patients.

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การเพิ่มการกำจัดโดยการใช้ผงถ่านกัมมันต์ซ้ำหลายครั้งในภาวะวาวโปอิค แอซิคเป็นพิษฉับพลัน

สุดา วรรณประสาท, สมศักดิ์ เทียมเก่า, ทวี ศิริวงศ์, นวนันท์ ปิยะวัฒน์กูล

การใช้ผงถ่านกัมมันต์ซ้ำหลายครั้งเป็นวิธีในการกระตุ้นการขจัดออกของสารพิษ อย่างไรก็ตามข้อมูลในการรักษาภาวะยาวาวโปอิค แอซิคเกินขนาดด้วยวิธีนี้ยังเป็นที่ถกเถียงกันอยู่ รายงานผู้ป่วยที่เกิดภาวะยาวาวโปอิค แอซิคเกินขนาดและประสบผลสำเร็จในการรักษาด้วยการใช้ผงถ่านกัมมันต์ซ้ำหลายครั้ง ค่าครึ่งชีวิตของยาวาวโปอิค แอซิคลดลงจาก 12 ชั่วโมง เหลือ 8 ชั่วโมง ระหว่างการรักษา ซึ่งพบว่าการรักษาด้วยผงถ่านกัมมันต์ซ้ำหลายครั้งสามารถกระตุ้นการขจัดออกของสารพิษได้เร็วเป็น 4 เท่าเมื่อเทียบกับการไม่ให้ผงถ่านกัมมันต์ ดังนั้นการให้ผงถ่านกัมมันต์ซ้ำหลายครั้งควรได้รับการพิจารณาให้เป็นการรักษาภาวะยาวาวโปอิค แอซิคเกินขนาด