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Clinical Analysis of Hyperammonemia by Perioperative Sodium Valproate Injection Application in Neurosurgery Patients

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Abstract

Introduction: Valproate injection is commonly used during perioperative period in neurosurgery department. Hyperglycemia induced by this drug can lead to hyperammonia-encephalopathy. This article aims to investigate the relationship between hyperammonemia and the perioperative application of sodium valproate injection.

Material and Methods: The blood ammonia status and other clinical features of perioperative patients from January to June 2019 were collected and retrospectively analyzed according to inclusion criteria.

Results: A total of 62 patients were enrolled, in which 37 patients in the hyperammonemia group and 25 patients in the normal group. There were significant differences in pre-ALT and pre-DBIL between the two groups. Blood drug concentration of valproate differentiated between the two groups. Three patients in the hyperammonemia group developed acute confusion. Except for blood ammonia, all the values of testing indicators were within the normal range. There was a moderate positive correlation between ALT and blood ammonia level in the hyperammonemia group.

Conclusion: Although liver function index and plasma concentration of valproic acid are related to the increase of blood ammonia, safe treatment range may not be able to avoid the occurrence of potential adverse events. It is recommended to enhance monitoring.

Keywords: Valproate; Hyperammonemia; Drug concentration; Therapeutic drug monitoring

Introduction

Valproate injection is a commonly used anti-epileptic drug during perioperative period in neurosurgery department. Hyperglycemia induced by this drug can lead to over-excitation of N-methyl-D-aspartate receptor, which can further decrease the threshold of epilepsy, induce edema and other adverse consequences, namely hyperammonia-encephalopathy [1]. These Clinical manifestations can easily be confused with common adverse events after neurosurgery like intracranial hemorrhage, ischemia, electrolyte or hormone levels disorder, status epilepticus etc. Misdiagnosis can result in poor outcomes [2]. This article retrospectively analyzed the blood ammonia status and other clinical features of perioperative patients using valproate injection to prevent epilepsy. Patients were divided into hyperammonemia group and normal group. Risk factors and relevance factors were analyzed.

Materials and Methods

Perioperative patients were selected from the Department of Neurosurgery, from January 2019 to June 2019. Inclusion criteria: (1) Age > 18 years old; (2) Valproate injection was used from the day 1 before surgery to postoperative period (at least 5 days). (3) Valproic acid blood concentration was obtained; (4) Simultaneous detection of blood ammonia value and liver (ALT, AST, TBIL, DBIL), kidney (Scr) function indictors, and serum albumin vale (ALB) on the same day as valproic acid blood concentration detection (TDM). Exclusion criteria: (1) Preoperative diagnosis of epilepsy or long-term use of valproic acid; (2) Data incomplete; (3) Combined use of other anti-epileptic drugs (4) Combined use of drugs that may lead to blood ammonia increasing; (5) Using parenteral nutrition or amino acid injection; (6) Combined use of sedative drugs; (7) Detectable factors that can cause consciousness disorder such as severe electrolyte, blood glucose or hormone levels abnormal.

Base line characteristics of patients, liver and kidney function index and serum albumin vale before and after injection of valproate were collected. The blood biochemical indicators were measured by the clinical laboratory according to the laboratory standard operating procedures. Patients were divided into hyperammonemia group (>30 μmol/L) and normal group (9-30 μmol/L) according to blood ammonia. The valproic acid plasma concentration was determined by chemiluminescence by using the i1000 analyzer and the valproic acid kit (Abbott Laboratories, USA).

Statistics

Statistical analysis was conducted on SPSS Statistics 24 (IBM corporation, USA). Data of normal distribution was expressed as "mean±SD" while the non-normal parameters as "median (Q25, Q75)". Cross-group comparison was achieved through Student's T test and Mann-Whitney U test, respectively. Bivariate correlation analysis was applied through Pearson's or Spearman's correlation tests. $P<0.05$ was reckoned to be of statistical significance. Risk factor identification for hyperammonemia was selected using logistic regression analysis. Outcome indexes and potential risk factors were predefined as dummy variables. Outcome indexes, "non-hyperammonemia group"=0, "hypernatremia group"=1; potential risk factors: "female"=0, "male"=1; "age<65"=0, "age>65"=1; "BMI<18.5"=0,

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"18.5<BMI<23.9"=1; "BMI>23.9"=2. Thereafter, identification of hyperammonemia after neurosurgery could be visualized with the potential risk factors and their respective weights, which might also helped with the screening for high-risk patients.

Results

A total of 62 patients were enrolled in the study, including 37 patients in the hyperammonemia group and 25 patients in the normal group. The basic characteristics, liver and renal function index, and serum albumin value are shown in Table 1, in which pre- means before operation. There was a significant difference in pre-ALT and pre-DBIL between the two groups ($p<0.05$), and no difference in other indicators.

	Hyperammonemia (n=24)	Normal (n=22)
Ammonia (μmol/L)*	36.81 (34.22,59.24)	23.32 (15.35,27.75)
Gender (F:M)	14:10	10:22
Age	54.97±14.82	51.85±15.39
BMI	24.09 (22.26,25.51)	23.41±3.52
pre-ALT (U/L)*	14.82 (10.45,18.61)	19.67 (15.45,23.17)
pre-AST (U/L)	15.73 (12.95,19.86)	16.52 (14.79,19.65)
pre-TBIL (μmol/L)	10.24 (7.45,12.46)	10.33 (8.75,12.55)
pre-DBIL (μmol/L)*	2.96±1.23	2.51 (1.75,2.85)
pre-ALB (g/L)	40.3 (34.2,44.2)	40.2 (29.5,43.5)
pre-Scr (μmol/L)	62.04±12.07	71.42±17.37
ALT (U/L)	13.9 (9.8,15.6)	13.2 (9.9,22.2)
AST (U/L)	16.1 (12.1,20.6)	25.6 (13.3,40.9)
TBIL (μmol/L)	12.14 (8.25,13.95)	10.78±3.83
DBIL (μmol/L)	3.56±1.62	3.25±1.38
ALB (g/L)	36.4 (33.1,39.8)	34.92±3.23
Scr (μmol/L)	55.14 (48.15,64.75)	63.23 (55.45,82.25)

Table 1: Basic characteristics of patients

The daily dose and blood concentration of valproate were shown in Table 2. There was a significant difference in the blood concentration between the hyperammonemia group and the normal group ($p<0.05$), although no difference in total dose (until detect day) and daily dose.

	Hyperammonemia (n=37)	Normal (n=25)
Ammonia (μmol/L)	36.81 (34.22,59.24)	23.32 (15.35,27.75)
TDM (μg/mL)*	62.79±17.25	55.72±22.77
Total Dose (mg)	3600 (2300,6000)	2400 (1200,6700)
Dose (mg/kg/d)	17.91±3.43	16.44 (13.83,18.86)

Table 2: Daily dose and TDM of valproic acid

Discussion

The mechanism of valproic acid-induced blood ammonia elevation has not been fully identified [3]. Possible mechanisms involve (1) valproic acid inhibits carbamoyl phosphate synthase-1 (CPS-1) in the liver, reduce intrahepatic ammonia metabolism, leads to elevated blood ammonia; (2) Glutamine plays an important role in immobilizing and transporting ammonia in the brain tissue. Valproic acid and its metabolites increase the transport of glutamine through mitochondrial membrane in the kidney, leading to an increase of free ammonia systematically; (3) valproic acid can increase excretion of carnitine through the urine and inhibit the reabsorption and transport of carnitine. This may affect the urea cycle in liver and further increase ammonia production. (4) gene defect in urea synthesis may have influence in valproic acid-induced blood ammonia elevation. The main cause of encephalopathy is induced by high blood ammonia, which stimulates the synthesis of glutamine in the brain, resulting in increased osmotic pressure in astrocytes, causing cell swelling and cerebral edema.

Our study found that the incidence of hyperammonemia occurred in 59.68% patients (37/62), similar to the previously report 16-52% [4]. Three patients developed acute disturbance of consciousness (4.48%). The incidence of valproate encephalopathy reported differently in literatures [5, 6], which may be related to the discrepant diagnostic criteria [7]. However, there are few research involve patients during neurosurgical operation. Various factors can result in disturbance of consciousness after neurosurgery, such as intracerebral hematoma, edema, electrolyte imbalance, brain stem injury, anesthetic drugs, etc., Hyperammonemia encephalopathy is difficult to diagnose in time, which may lead to serious consequences. Simultaneous use of sedatives and other antiepileptic drugs has been shown to increase the toxicity of valproic acid. Thus, our study excluded patients with combination therapy. Patients with a hereditary or dietary carnitine deficiency or urea cycle enzyme deficiency also prone to develop valproate encephalopathy, but this etiological factor is rarely pre-screened in clinical practice [8]. The relationship of liver function, blood concentration of valproate and hyperammonemia was reported incompatible among articles. Some reports these factors are not clearly related to hyperammonemia [9], while others found that blood ammonia levels are correlate to valproic acid plasma concentration and liver function [10]. Abnormal liver function may also occurs after valproic acid concentration and blood ammonia values return to normal [11]. Our study found that pre-operation liver function indicatiors (pre-ALT, pre-DBIL) and value of valproic acid blood concentration were significantly different between the hyperammonemia group and normal group (p 0.05). In the hyperammonemia group, there was a moderate positive correlation between liver function index (ALT) and blood ammonia level ($\rho=0.422$, $p=0.40$). Despite this, the value of liver function and blood concentration in all patients were within the normal range. Since the increase of blood ammonia level is likely to occur in the background of normal liver function and blood concentration of valproic acid are also within the normal range, it is recommended that when application valproic acid, blood ammonia test should be performed immediately if there are symptoms of encephalopathy, consciousness changes, stagnation, etc.

Consistent with previously reports, patients experienced valproate encephalopathy can restored quickly after timely drug withdrawal with of without using of ammonia excretion stimulants. Few neurological sequela left with immediate treatment [12]. It is reported that only use ammonia excretion stimulants like lactulose, probiotics or levocaniting to decrease the blood ammonia levels with dose reduction of valproic acid can also solve the symptoms. This may further indicate that blood ammonia levels may be related to valproic acid plasma concentrations [13]. However, as in this study, several studies reported, in patients with hyperammonemia, valproic acid plasma concentrations are within the normal range [14]. Thus the correlation and influencing factors need further study. In addition, the impact of asymptomatic hyperammonemia on long-term prognosis still lacks sufficient data [15].

The limitations of our study are a relatively small sample size and it is a retrospective analysis. However, unlike other studies, we exclude lots of

factors that may influence blood ammonia level and those may change valproic acid blood concentration. Thus, the results of our study may show the real relationship of valproate and hyperammonemia.

Conclusion

Valproate injection is a commonly used anti-epileptic drug among perioperative patients in neurosurgical department. The side effect of valproate such as liver injury and coagulopathy has been fully studied. When it comes to hyperammonemia and encephalopathy, few factors can be used to predict this tough problem. Symptoms of hyperammonemia-encephalopathy are easily confused with other events among perioperative patients, which may lead to misdiagnosis and poor outcomes. This study has rigorously inclusion and exclusion criteria to try to explore the differences between patients with hyperammonemia and the normal one. We found that compared with the normal group, the patients with hyperammonemia had higher baseline liver function indexes (pre-ALT, pre-DBIL) and higher valproic acid plasma concentrations. Correlation analysis found that, liver function indicators after operation (ALT) have a moderate positive correlation with blood ammonia levels. However, all these values of patients are within the normal range, indicating that safe treatment does not necessarily avoid the occurrence of potential adverse events. For those developed acute disturbance of consciousness, symptoms improved rapidly after withdrawing or reducing the dose and using ammonia excretion stimulants, but the effect of asymptomatic hyperammonemia on the long-term prognosis still needs further study. Further large sample studies are needed to determine the influencing factors and prognosis of valproate encephalopathy.

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