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RESEARCH PROGRESS ON CLINICAL APPLICATION AND SAFETY MANAGEMENT OF TOPIRAMATE

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Abstract: Topiramate is a broad-spectrum anti-epileptic drug (anti-epileptic drugs, AED) with multiple mechanisms of action, which is widely used in the treatment of various types of epilepsy and epilepsy syndromes. How to correctly select effective AEDs and balance the relationship between drug efficacy and adverse reactions has always been a key issue in clinical practice. This article describes the research progress of topiramate's clinical application, mechanism and safety management, including cognitive impairment, nephrolithiasis and sudomotor dysfunction. This article reviews the research progress on the clinical application and safety management of topiramate, including cognitive impairment, kidney stones and sudomotor dysfunction.
Keywords: Topiramate; Epilepsy; Clinical application; Safety management

1 CLINICAL APPLICATION OF TOPIRAMATE

Topiramate is widely used clinically as monotherapy or in combination for generalized tonic-clonic seizures and focal seizures (with or without generalized seizures) in adults and children [1]. In addition, topiramate can be used as an add-on therapy for drug-refractory epilepsy [2], juvenile myoclonic epilepsy (JME) [3], epileptic encephalopathy (West syndrome [4], Dravet syndrome [5] and Lennox - Treatment of Gastaut syndrome [6]).
Studies have shown that when topiramate monotherapy treats epilepsy (including generalized tonic-clonic seizures and focal seizures, etc.), the seizure -free rate of patients after 6-7 months is 44%-83%, and after 12-13 months of treatment The seizure- free rate ranges from 41% to 76%. Subgroup analysis shows that topiramate is effective for both children and elderly patients [1]. An evidence-based systematic review of 12 randomized, placebo-controlled trials (1650 patients) showed an overall risk ratio (RR= 2.71, 95% CI: 2.05-3.59), and the proportion of seizure- free patients increased compared with placebo-treated patients, the difference was statistically significant (RR=3.67, 95%CI: 1.79-7.54) [2]. Liu et al[3] included 3 randomized controlled trials (83 cases), analyzed and compared the proportion of patients with JME or primary generalized tonic-clonic seizures reduced by ≥ 50% or the proportion of seizure-free patients, suggesting that the efficacy of topiramate was comparable to that of valproex. Compared with valproic acid, the difference was not statistically significant, and the tolerance was better than valproic acid.
In a systematic review of 14 studies, 2 were randomized controlled studies, 9 prospective studies and 3 retrospective studies. Except for 1 randomized controlled study, the results of other studies support the use of topiramate in the treatment of West syndrome; 9 prospective studies support the use of topiramate as the first-line or add-on treatment of West syndrome, and the seizure-free rate of epilepsy patients ranges from 17% to 40 %. %, 45% to 70% of patients were treated effectively (reduction in seizure frequency ≥ 50%)[4]. Studies have reported that topiramate is effective in the treatment of Dravet syndrome, with a response rate of 35% to 78%, and 10% to 17% of patients who have been seizure-free for at least 4 months[5,7]. Topiramate is also one of the recommended AEDs for the treatment of Lennox-Gastaut syndrome[6]. Studies have shown that compared with the placebo group, topiramate can significantly reduce the incidence of falls in patients (compared with the baseline, the topiramate group decreased by 14.8%; the placebo group increased by 5.1% %, P=0.041) [8].

2 MECHANISM OF ACTION OF TOPIRAMATE

The imbalance of excitatory and inhibitory neuron activities is the main pathogenesis of epilepsy, and ion channels are the basis of excitatory regulation in vivo, and the changes in their structure and function lead to the disturbance of excitatory regulation, thereby inducing epilepsy. Ion channels can be divided into voltage-gated ion channels and ligand -gated ion channels according to their characteristics. Many studies have proved that the two are closely related to epilepsy [9]. Voltage-gated Na+ channels play an important role in the generation of action potentials, and the SCN1A, SCN2A, and SCN8A genes encoding different Na+ channel subtypes are causative genes that lead to epilepsy, for example, the SCN1A gene-related Dravet syndrome [10]. Voltage-gated Ca2+ channels are involved in important physiological processes in the body, regulating nerve excitability and synaptic transmission; different types of Ca2+ channel dysfunction can lead to different types of epileptic seizures, for example, abnormal T-type Ca2+ channels are associated with absence seizures[11]. Glutamate (Glu) is the most important excitatory neurotransmitter in the central nervous system. It is widely distributed in the central nervous system and is closely related to epilepsy. Various mechanisms lead to epilepsy through the Glu transmitter and its receptor pathway [12]. γ-aminobutyric acid (γ-aminobutyric acid, GABA) is the main inhibitory neurotransmitter in the central nervous system of mammals, widely

distributed throughout the nervous system, and plays an important role in the pathogenesis of epilepsy ; GABAA receptors (GABAAR) is a ligand-gated ion channel, and epilepsy- associated gene mutations are widely expressed in the α, β, γ, and δ subunits of GABAAR [13].

Topiramate has multiple anti-epileptic mechanisms, and exerts anti-epileptic effects by acting on different ion channels, neurotransmitters and receptors [14]: ① exerts anti- epileptic effects by blocking Na+/Ca2+ channels ; ② acts on GABAAR to enhance GABA-mediated ③Action on α-amino-3-carboxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and kainate receptor (kainite receptor) of glutamate receptor (GluR), KAR) subtype, reduce the excitatory effect mediated by Glu; ④ as an inhibitor of carbonic anhydrase, regulate the concentration of protons to control the excitability of GluR and regulate the transmission of GABAergic neurons to play an anti-epileptic effect. In addition, topiramate may be involved in reducing body mass through the mechanism of action of inhibiting carbonic anhydrase [15]. It has also been found that inhibition of carbonic anhydrase is associated with an increased risk of kidney stones and metabolic acidosis [16].

3 SAFETY MANAGEMENT OF TOPIRAMATE

3.1 Topiramate Affects the Management of Cognitive Function

Cognitive function refers to the process in which the human brain receives external information and converts it into internal psychological activities after processing, so as to acquire knowledge or apply knowledge. Cognitive functions include memory, language, visual space, executive, Calculation, understanding and judgment etc. [17]. Studies have found that up to 70% of untreated new-onset epilepsy patients have cognitive impairment, which affects multiple cognitive areas of patients, including memory, attention, and executive function, etc. [18]. There are many reasons for cognitive impairment in patients with epilepsy. Factors related to cognitive impairment in epilepsy include: seizures, interictal epileptiform discharges, brain lesions, genetic factors, social and psychological factors, and the influence of AEDs, etc.[19]. Among them, the influence of epilepsy- related factors and brain lesions play an important role in the cognitive impairment of epilepsy [20].

Cognitive adverse reactions of topiramate reported in the literature mainly include difficulty in finding words, decreased concentration and decreased memory, etc. [21]. Different studies have reported that the incidence of cognitive adverse reactions of topiramate is somewhat different, most of which are mild to moderate and transient, and usually occur during the dose-increasing period (4-8 weeks). After continuing treatment or stopping the drug, the adverse reactions usually disappear Improve or disappear, so the probability of discontinuation due to cognitive adverse reactions is low[22-24].

3.1.1 Topiramate has a dose-dependent effect on cognitive impairment

A double-blind, placebo-controlled, parallel-controlled, 24-week study by Loring et al. [25] showed that the cognitive impairment of topiramate was dose-dependent, including 188 adult patients with normal cognitive function. The CNTB assesses cognitive functions, including attention, information processing speed, verbal learning, memory, and spatial memory, among others. After 24 weeks of treatment with topiramate doses of 96, 192 and 384 mg·d-1, the proportions of patients with cognitive impairment were 8%, 15% and 35% respectively; topiramate dose 192 mg·d-1 group ($P<0.01$) and 384 mg·d-1 group ($P<0.000\ 1$) had significantly higher incidence of cognitive impairment than placebo group (incidence of cognitive impairment was 5%).

Stefan et al[26] carried out a 1-year open-label, flexible-dose study, including 107 elderly patients with epilepsy, and showed that the incidence of memory impairment (8.5%) with topiramate add-on therapy (average dose 153 mg·d-1) was lower than that with simple dose. The incidence rate (2.1%) of drug treatment (mean dose 98 mg·d-1) was high. A meta-analysis by Quan Shuyan et al.[27] focused on 9 literatures (3 randomized controlled articles and 6 case series reports), including 1 240 children with epilepsy or migraine, and the control group was placebo (Kamasi Pinghe valproic acid), the dose of topiramate is 50 mg·d-1, 100 mg·d-1 or 4-9 mg·kg-1·d-1), the results show that the topiramate treatment of children with epilepsy has cognitive impairment, But the incidence is low. The main manifestations include: Psychomotor disturbance and difficulty concentrating, the incidence rates were 0.08 (95%CI: 0.02-0.26) and 0.07 (95%CI: 0.02-0.21) respectively; the incidence rates of memory loss and language impairment were different Not statistically significant. When the dose of topiramate reaches 100 mg·d-1, it may slightly prolong the motor reaction time, but has no significant effect on memory.

3.1.2 Topiramate-related cognitive impairment usually occurs during the dose-increasing period, and most of them are mild to moderate and transient

Studies have shown that cognitive impairment with topiramate usually occurs during the boost phase. An open, retrospective study by Lu et al[23] included 227 Chinese adults with epilepsy who were treated with topiramate 100-200 mg·d-1 for an average of (10.3±6.9) months, and found that most cognitive The damage appeared during 4-8 weeks of treatment, and most of them were mild to moderate and transient. A double-blind, placebo-controlled study by Zhang et al[24] included 86 elderly patients with refractory and focal epilepsy, and topiramate 200 mg·d-1 was added to the treatment for 20 weeks, and found that cognitive impairment included memory impairment, language Impairment and psychomotor retardation adverse effects occurred during the ramp-up phase (first 8 weeks); >90% of neurologic adverse

effects (including cognitive impairment) were assessed as mild to moderate by investigator; >80% were transient, continued Adverse reactions were relieved after topiramate treatment.

3.1.3 Topiramate-related cognitive impairment is reversible

Studies have found that after cognitive impairment occurs during topiramate treatment, the cognitive impairment can be improved by reducing the dose or stopping the drug. A retrospective study conducted by Thompson et al[28] included 18 adult patients with epilepsy. After topiramate (median dose 300 mg·d-1) was added to the treatment, the patients' speech fluency and speech learning ability were affected, but in Verbal fluency, verbal learning ability, and digit span test results improved after topiramate dose reduction or discontinuation.

It is worth noting that the study by Jung et al. [29] found that topiramate could improve some cognitive impairment in children with epilepsy. The study included 664 children with epilepsy, and the dose was 12.5-50 mg·d-1 for body weight <30 kg; Body weight > 30 kg: 75-100 mg·d-1, compared with before treatment with topiramate treatment for 6 months, cognitive impairments such as memory, language and attention were significantly improved. 3.1.4 Possible predictors of topiramate-related cognitive impairment Working memory capacity (working memory capacity, WMC) is the capacity to temporarily process and store limited information, and there are individual differences in WMC. The double-blind placebo-controlled cross-over study conducted by Callisto et al.[30] and Barkley et al.[31] included 46 and 29 healthy volunteers respectively. The results showed that the degree of topiramate-related cognitive impairment was regulated by its plasma concentration and WMC, After correcting for differences in WMC, 1 μg·mL-1 topiramate plasma concentration can lead to a 3.6% reduction in the accuracy of all memory loads, and the cognitive impairment is lower in the high WMC group, and the WMC group is more severe, and the increase in plasma concentration more sensitive. Therefore, WMC may be one of the predictive factors for topiramate's impact on cognitive function, but the research objects included in this research project were all healthy people, and further observation and research in epilepsy patients are needed.

At present, many studies have shown that topiramate-related cognitive impairment is mainly related to high-dose, rapid dose increase and multi-drug combination therapy. Therefore, when using AEDs (including topiramate alone or in combination), the following principles should be followed to help reduce the risk of cognitive impairment: ① Choose a lower effective dose that can control seizures, and start with a small dose; ② Feasible ③Consider the pharmacokinetic characteristics (such as choosing a sustained-release dosage form to avoid a higher peak serum drug concentration); ④If multi-drug combination therapy is required, when choosing AEDs combined with topiramate, you should Consider drug interactions and the impact on patients' cognitive impairment, and reduce the drug load as much as possible. Clinicians should inform patients and (or) family members of the possible cognitive impairment associated with the use of AEDs, which will help early identification, follow-up, and treatment of cognitive impairment caused by related AEDs. It is recommended to screen patients' cognitive function before and after starting AEDs treatment to guide treatment decisions and reduce the occurrence of cognitive impairment [32].

3.2 Management of Kidney Stones

Studies have shown that the incidence of kidney stones varies with race, climate and diet [33]. In the research and development phase of adding topiramate to the treatment of epilepsy, 1.5% of adults exposed to topiramate reported kidney stones, and the incidence rate was 2 to 4 times higher than that of the untreated population; Renal stones have been reported in humans [34]. At present, the research samples of children with kidney stones after using topiramate are small. Mahmoud et al. [35] reported (Saudi Arabia) 96 children who had been treated with topiramate for ≥ 1 year and found that 5 children (5.2%) developed kidney stones. In another study (USA) of 41 children treated with topiramate for an average of 27 months, asymptomatic nephrolithiasis was found in 2 patients (4.8%) [36].

Data from China show a lower incidence of topiramate-associated kidney stones. A single-center retrospective study analyzed the correlation between the use of topiramate and the occurrence of kidney stones in children with epilepsy in Hong Kong, China. 81 children were included, and the dose of topiramate was 1.2-12.0 mg·kg-1·d-1; the average dose was 6 mg On d-1, the treatment duration ranged from 1.3 to 12.0 years (average 8.3 years). Kidney stones were found in 2 children who could not walk freely. The renal function tests were normal, and the kidney stones did not require active medical intervention; no other children were seen Kidney stones occurred [33]. A cohort study based on the population of Taiwan, China included 1 377 adult epileptic patients treated with topiramate and matched 1 377 patients who did not take topiramate. Survival analysis and Cox proportional hazards regression analysis were used to evaluate the risk of urinary calculi caused by topiramate. The results It was found that the proportion of urinary calculi in all patients within 2 years was 2.9%, and the difference between the two groups was not statistically significant (P=0.138). There was a previous history of urolithiasis [37].

Possible mechanism for the development of nephrolithiasis: Topiramate inhibits carbonic anhydrase, reduces filtered bicarbonate reabsorption, increases renal tubular citrate reabsorption, resulting in a decrease in urinary citrate. Hypocitraturia and inappropriate acidification of urine increase the risk of stone formation. In addition, if patients have risk factors such as hypercalciuria, hyperoxaluria, and increased urinary sodium secretion, they can also promote stone formation [38].

Management strategies to prevent topiramate-related kidney stones include: ① Supplementing citrate preparations can effectively increase urinary citrate levels, reduce stone formation and increase stone excretion rate; ② Drink more water, which has a preventive effect on people with a high risk of stones; ③Avoid combination therapy, such as combined use of topiramate and any other drug that produces metabolic acidosis; ④For patients with stones and history of renal tubular acidosis, topiramate should not be used, and if persistent renal tubular acidosis occurs, it is recommended to stop using it Topiramate [39,40].

3.3 Management of Sweating Disorders

A domestic multi-center clinical study reviewed the curative effect and safety monitoring of topiramate after listing in China, observed the clinical data of 10 106 epileptic patients, and showed that the overall incidence of sweating disorders was 3.74%, and the incidence rate in children (5.50%) was higher. in adults (0.37%). Gender, seizure frequency, addition of other AEDs, and curative effect did not affect the occurrence of sweating disorders; patients with younger ages and higher doses were more prone to sweating disorders in summer[41]. The characteristics of sweating disorder induced by topiramate include: ① age-related, younger children are higher than older children, and older children are higher than adults; ② generally occur in the late period of increasing dose and early stable period; ③ positive correlation with dose; ④ Most of them are temporary, and can disappear or alleviate naturally after several months [42].

Patients taking topiramate, especially children, should be closely monitored for symptoms of decreased sweating and increased body temperature, especially in hot weather. Caution should be exercised when topiramate is prescribed concomitantly with other drugs capable of causing heat-related illness in patients. These drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity [34].

If the patient has sweating disorder, it can be relieved naturally after lowering the ambient temperature or reducing the dose. Strenuous outdoor activities should be reduced, avoid sunlight, try to learn and play in a cool environment, and take frequent baths or warm water baths. Do not use antibiotics, do not use antipyretics. Under normal circumstances, there is no need to stop the drug to avoid seizures caused by drug withdrawal or drug change [43,44].

4 EPILOGUE

In summary, topiramate has multiple mechanisms of action, exerts antiepileptic effects by acting on different ion channels, neurotransmitters, and receptors, and can be used for generalized tonic-clonic seizures and focal epileptic seizures in adults and children (with or without generalized seizures) as monotherapy or add-on therapy, it can also be used for add-on therapy of refractory epilepsy and the treatment of epileptic encephalopathy and JME. Topiramate, as a broad-spectrum AED, has a good effect on many types of epilepsy and epilepsy syndromes. Cognitive impairment related to topiramate is dose-dependent, mostly occurs in the dose-increasing period, and most of them are mild to moderate and transient, and the discontinuation rate due to cognitive impairment is low; kidney stones and sweating disorders during topiramate treatment less common. Clinically, reasonable management of AEDs can help reduce the occurrence of the above-mentioned adverse drug reactions, better play the role of topiramate in the treatment of epilepsy, and improve the quality of life of patients.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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