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唑尼沙胺单药治疗儿童癫痫疗效及骨代谢的影响*

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摘要 目的:探讨唑尼沙胺(Zonisamide ZNS)对儿童癫痫疗效及骨代谢的影响。方法:选择2013年3月至2014年3月到河北省儿童医院神经内科门诊及病房就诊的新诊断癫痫患儿,其中男性36名,女性24名,年龄在2-14岁,给予唑尼沙胺单药治疗,分别于服药前、服药后6月查血甲状旁腺素、血钙、磷、碱性磷酸酶和骨密度测定,并与对照组进行对比。对照组选择就诊于儿保科年龄、性别相匹配的正常儿童。并分析癫痫患儿发作频率及严重程度,评估疗效。结果:唑尼沙胺治疗53例癫痫患儿中,42例(79.2%)无发作,8例(15%)有效,3例(5.7%)无效。且对骨代谢相关血清学指标、骨密度无明显影响。结论:ZNS对儿童癫痫有显著疗效,是一种广谱、耐受良好的抗癫痫药。

关键词 唑尼沙胺;癫痫;疗效;骨代谢

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Clinical Efficacy of Zonisamide Monotherapy and Its Effect on Bone Metabolism of Epilepsy Children*

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ABSTRACT Objective: To study the influence of zonisamide (ZNS) on the curative effect of epileptic children and their bone metabolism. Methods: The newly diagnosed epilepsy patients in our hospital were selected in this study, including 36 male and 24 female, aged from 2 to 14 years old. They were given zonisamide monotherapy. And their blood parathyroid hormone, calcium, phosphorus, alkaline phosphatase and bone mineral density were detected respectively before taking the medicine, at 6 months after taking this medicine. Data were compared with that of the control group. The age and gender matched normal children from our children's health department were selected as control group. Analyze the epilepsy seizure frequency and severity of children and evaluate the curative effect. Results: Among the 53 epilepsy children treated with zonisamide, 42 cases (79.2%) had no attack, and 8 cases (15%) got curative effect. Zonisamide was invalid for 3 patients (5.7%). It had no obvious effect on the bone metabolism related serological indexes and bone mineral density. Conclusion: ZNS have remarkable curative effect on children epilepsy. Therefore, it is a kind of broad-spectrum antiepileptic drugs and can be well tolerated.

Key words: Zonisamide; Epilepsy; Curative effect; Bone metabolism

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前言

癫痫是以脑正常电活动自发性周期性破坏的结果而导致的反复发作为特征。7岁以内起病者占小儿癫痫总数的82.2%。婴幼儿期是癫痫发作的第一个高峰时期[1,2]。我国儿童癫痫的年发病率为151/10万,患病率为0.345%[3]。目前以长期口服抗癫痫药物治疗为主,首次单药治疗能使50%癫痫发作得到控制[4]。唑尼沙胺是一种新型抗癫痫药,对于儿童疗效及骨代谢是否有影响报道较少。本研究通过分析儿童癫痫疗效及骨代谢指标的变化,探讨唑尼沙胺在儿童癫痫使用过程中的有效性、安全性、耐受性。

1 资料和方法

1.1 临床资料

选取2013年3月至2014年3月在河北省儿童医院神经内科新诊断的癫痫患儿,入组对象为年龄>2岁;生长发育、日常活动量正常;入组前2个月内癫痫发作2次以上(符合国际抗癫痫联盟癫痫分类标准,且未服用抗癫痫药物)。除外内分泌疾病、进行性中枢神经系统疾病或严重全身性进行性疾病及使用激素或其他影响骨骼系统代谢药物治者。

1.2 用药方法与标本采集

给药标准程序:即大约每日2 mg/kg,分二次口服。当发作无改变或仅部分减少时,剂量每1-2周增加1-2 mg/kg,只要无

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不可接受的副作用，可增加至最大量 12 mg/kg。

在上午 8-9 点抽取空腹静脉血，立刻送检血钙、血磷、碱性磷酸酶、甲状旁腺素测定，进行骨代谢生化指标测定。

1.3 骨密度测量

采用 Sunlight Omnisense TM 7000P 定量超声仪（以色列 Sunlight 公司），测量左侧胫骨中段及桡骨远端的骨密度。

1.4 疗效评估

临床疗效以患儿临床发作次数减少的比例判断。完全控制：无临床发作，显效：临床发作控制 75%以上，有效：临床发作减少 50%以上，无效或恶化：临床发作减少低于 50%，总有效率：（完全控制 + 显效 + 有效）/ 总例数 *100%。

1.5 统计学处理

以均数 $\bar{x}\pm s$ 表示。组间比较用 t 检验，两个以上样本均数比较采用单因素方差分析。以 $P<0.05$ 差异有统计学意义。

2 结果

使用唑尼沙胺治疗 53 例癫痫患儿中，42 例（79.2）无发作，8 例（15%）有效，3 例（5.7%）无效（表 1）。实验组治疗前、治疗后 6 个月骨代谢相关指标比较（$P>0.05$）。实验组治疗前、治疗后 6 个月骨代谢相关指标与对照组同期之间比较（$P>0.05$）（表 2）。表明唑尼沙胺单药治疗新诊断癫痫起效迅速，临床疗效显著，对各个发作类型疗效较好。且耐受性好，对骨代谢指标无影响。

表 1 唑尼沙胺单药治疗 6 个月时发作控制情况

Table 1 The control of seizure six months after zonisamide monotherapy

Seizure type	Cases	No attack	Effective	Nullity
Simple partial seizure	5	4 (80%)	1 (20%)	0
Complex partial seizure	7	(71%)	1 (14%)	1 (14%)
Part of the secondary comprehensive attack	24	20 (83.2%)	3 (12.5%)	1 (4.1%)
Tonic clonic seizure	11	10 (90.9%)	1 (9.1%)	0
Absence seizure	6	3 (50%)	2 (33%)	1 (17%)
Total	53	42 (79.2%)	8 (15%)	3 (5.7%)

表 2 唑尼沙胺组治疗前后与对照组各项骨代谢指标比较（$\bar{x}\pm s$）

Table 2 Comparison of the bone metabolism indexes in zonisamide group before and after treatment and control group（$\bar{x}\pm s$）

Indicators	Zonisamide group		F	P	Control group	
	Before treatment	6 months			After treatment	6 months
Ca (mmol/L)	2.46± 0.12	2.43± 0.06	0.5	>0.05	2.44± 0.10	2.46± 0.08
P (mmol/L)	1.50± 0.18	1.63± 0.17	0.62	>0.05	1.54± 0.16	1.50± 0.19
ALP (U/L)	187.37± 38.78	185.26± 34.53	0.27	>0.05	184.71± 39.54	187.31± 41.02
BAP	234.01± 15.76	231.51± 16.17	0.50	>0.05	234.11± 1359	233.40± 14.32
PTH(pg/ml)	3416± 14.48	4107± 14.96	0.57	>0.05	34.81± 15.06	35.06± 13.69
BMD	2.32± 1.98	2.26± 1.926	0.18	>0.05	2.218± 1.76	2.09± 1.78

3 讨论

唑尼沙胺（Zonisamide，ZNS）是一种新型抗癫痫药物，具有安全、有效、耐受性良好等优点，在临床上应用越来越广泛[5,6]。唑尼沙胺作用于大脑多个位点，其主要作用机制与抑制 NA+ 依赖动作电位的持续高频重复放电和降低 T - 型钙通道相关。现已明确，作用于钠离子通道和 T- 型钙离子通道抗癫痫药与单纯性、部分性、全面性强直 - 阵挛发作和失神发作有疗效[7,8]。因此，从唑尼沙胺在这些位点的药理活性可以预测到一个相似的广谱活性并且受临床支持[9]。唑尼沙胺也改变多巴胺、5- 羟色胺和乙酰胆碱的代谢。与其它抗癫痫药相比，唑尼沙胺对 GABA 功能没有明显作用[10]。给予唑尼沙胺伴有谷氨酸的释放，这些作用可能是间接地，由其对电压门控钠离子通道和钙离子通道的作用介导。唑尼沙胺作用机制中有潜在的神经保护作用[11,12]，可限制反复发作引起神经细胞损伤，在细胞和生化水平已证明唑尼沙胺的这种神经保护活性。临床应用：唑尼沙胺在多种癫痫综合征的作用是由多重作用模式所致，因为不同类型发作对不同作用模式有反应[13]；另外，这种广泛的作用机制可增加唑尼沙胺以互补的方式与其它同用抗癫痫药物发挥作用的可能性。为多种癫痫综合征治疗提供了一个好的选择[14]。

在临床应用证实，唑尼沙胺单药治疗对各种发作类型具有良好的疗效，耐受性好，不良反应少[15,16]。但是在对儿童部分癫痫伴或不伴继发全面性发作、失神发作等方面是否也有明显疗效，尚不清楚。有报道唑尼沙胺的不良反应率 39%[17]，本组实验有 6 例患儿出现了不同程度头痛、头晕、嗜睡、厌食，2 例易激惹及自发行为下降，未发现出汗少病例，绝大多数患儿服药 1 月后逐渐缓解，或者减少剂量后即可缓解，再次加量不再发生，无因严重不良反应终止治疗病例。有研究发现，长期服用抗癫痫药物对患儿骨代谢及骨骼发育有影响[18]，本组患儿治疗 6 个月，患儿骨密度未见明显改变，骨代谢生化指标无明显改变。

综上所述唑尼沙胺单药治疗新诊断癫痫起效迅速，临床疗效显著，对各个发作类型疗效较好。单药治疗对癫痫患儿骨密度及骨代谢无明显不良影响。由于唑尼沙胺在我国临床应用时间短，缺乏系统、大规模的临床研究，所以还需要进一步临床观察和动物实验研究，更加充分的认识唑尼沙胺。为癫痫患者减轻痛苦，提高他们的生活质量，寻找一种有效的、广谱抗癫痫

耐受性良好的药物。

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