·儿童和青少年癫痫·

奥卡西平活性代谢产物测定在儿童局灶性癫痫治疗中的应用

张培元　李惠芬　刘晓军　于晓莉　张玉琴

【摘要】 **目的**　探讨奥卡西平活性代谢产物10-单羟基卡马西平(MHD)血药浓度测定在儿童局灶性癫痫治疗中的应用价值。**方法**　共110例儿童局灶性癫痫患者于奥卡西平单药或药物联合治疗3个月后,采用高效液相色谱法测定MHD血药谷浓度。**结果**　110例患儿奥卡西平平均治疗剂量(25.52±7.28) mg/(kg·d),MHD中位血药谷浓度7.00(4.95,10.50) mg/L,89例(80.91%)<12 mg/L。Spearman秩相关分析,MHD血药谷浓度与奥卡西平治疗剂量呈正相关(r_s=0.337,P=0.000)。奥卡西平治疗剂量仅年长(>7岁)局灶性癫痫患儿低于年幼(≤7岁)患儿且差异有统计学意义[(23.13±5.56) mg/(kg·d)对(28.09±8.06) mg/(kg·d);t=3.778,P=0.000],而男性与女性(t=1.067,P=0.288)、药物难治性与非药物难治性(t=1.417,P=0.159)、单药治疗与药物联合治疗(t=1.671,P=0.098)组间差异无统计学意义;MHD血药谷浓度仅药物难治性局灶性癫痫患儿低于非药物难治性患儿且差异有统计学意义[6.32(3.05,8.58) mg/L对8.30(5.75,10.85) mg/L;Z=2.380,P=0.017],而男性与女性(Z=0.604,P=0.546)、年长与年幼(Z=0.179,P=0.858)、单药治疗与药物联合治疗(Z=1.583,P=0.113)组间差异无统计学意义。**结论**　MHD血药谷浓度与奥卡西平治疗剂量呈正相关关系;为达到相同的MHD血药浓度,年幼局灶性癫痫患儿应服用更大剂量的奥卡西平;奥卡西平治疗儿童药物难治性局灶性癫痫时,应根据MHD血药浓度及时调整药物剂量。

【关键词】 癫痫;　儿童;　卡马西平;　血药浓度;　色谱法,高压液相

Clinical application of blood concentration monitoring of active metabolite of oxcarbazepine in childhood focal epilepsy

ZHANG Pei-yuan[1], LI Hui-fen[2], LIU Xiao-jun[1], YU Xiao-li[1], ZHANG Yu-qin[1]
[1]*Department of Neurology, Tianjin Children's Hospital, Tianjin 300134, China*
[2]*Tianjin Institute of Pediatrics, Tianjin 300074, China*
Corresponding author: ZHANG Yu-qin (Email: zhangyuqin0809@sina.com)

【**Abstract**】 **Objective**　To investigate the value of blood concentration monitoring of 10-monohydroxy carbamazepine (MHD), the active metabolite of oxcarbazepine (OXC), in the treatment of childhood focal epilepsy. **Methods**　A total of 110 children with focal epilepsy took OXC for 3 months and then the MHD concentrations were determined by high pressure liquid chromatography (HPLC). **Results**　The average dose of OXC in 110 children was (25.52 ± 7.28) mg/(kg · d) and the valley point concentration of MHD was 7.00 (4.95, 10.50) mg/L, and 89 cases (80.91%) < 12 mg/L. A linear relationship between MHD valley point concentration and OXC dose (r_s = 0.337, P = 0.000) was shown by Spearman rank correlation analysis. The dosage of OXC for older (>7 years) children was significantly lower than that of younger (≤7 years) children [(23.13 ± 5.56) mg/(kg · d) vs. (28.09 ± 8.06) mg/(kg · d); t = 3.778, P = 0.000], while there was no significant difference between the concentration of children with different sexes (t = 1.067, P = 0.288), between children with and without drug resistant epilepsy (DRE; t = 1.417, P = 0.159) and between monotherapy and combination drug therapy (t = 1.671, P = 0.098). The MHD valley point

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作者单位:300134 天津市儿童医院神经内科(张培元、刘晓军、于晓莉、张玉琴);300074 天津市儿科研究所(李惠芬)
通讯作者:张玉琴(Email:zhangyuqin0809@sina.com)

concentration in DRE group was lower than that of non-DRE group [6.32 (3.05, 8.58) mg/L vs. 8.30 (5.75, 10.85) mg/L; Z = 2.380, P = 0.017], while there was no significant difference between the concentration of children with different sexes (Z = 0.604, P = 0.546), between older and younger children (Z = 0.179, P = 0.858) and between monotherapy and combination drug therapy (Z = 1.583, P = 0.113). **Conclusions** There is a linear relationship between MHD steady state valley point concentration and the dose of OXC. To achieve the same MHD level, the younger children need to take a larger dose of OXC. When OXC is used to treat drug resistant focal epilepsy in children, the dosage should be adjusted according to the monitoring of blood concentration of MHD.

【Key words】 Epilepsy; Child; Carbamazepine; Plasma concentration; Chromatography, high pressure liquid

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儿童癫痫约占全部癫痫的60%，最常见的发作类型是局灶性发作，国际抗癫痫联盟（ILAE）推荐奥卡西平（OXC）作为儿童局灶性癫痫的一线药物[1]。奥卡西平口服后迅速被肝细胞溶质芳基酮还原酶还原为主要活性代谢产物10-单羟基卡马西平（MHD），后者是研究奥卡西平药代动力学和药效学的靶向生物学标志物[2-3]。目前尚无MHD有效血药浓度参考值范围的一致性结论[4-6]，且个体化差异明显，如何通过MHD血药浓度指导奥卡西平在儿童局灶性癫痫中的应用，是临床医师面临的问题。本研究回顾分析110例采用奥卡西平治疗的儿童局灶性癫痫包括药物难治性癫痫患儿的临床资料，并测定MHD血药浓度，以期探讨该项生物学标志物指导奥卡西平临床应用的策略。

资料与方法

一、临床资料

1. 纳入标准 （1）局灶性癫痫符合2014年国际抗癫痫联盟提出的“癫痫”实用性定义[7]，发作类型和脑电图符合2017年国际抗癫痫联盟修订的新的分类标准[8]中局灶性发作。（2）药物难治性癫痫的诊断均符合2010年国际抗癫痫联盟提出的“药物难治性癫痫”定义，即应用正确选择且能够耐受的两种抗癫痫药物（单药或药物联合治疗）后仍未达到持续无发作[9]。（3）年龄≤16岁。（4）奥卡西平单药或添加治疗，加药前3个月平均癫痫发作频率≥1次/月。（5）本研究经天津市儿童医院道德伦理委员会审核批准，所有患儿或其家属均知情同意并签署知情同意书。

2. 排除标准 （1）合并其他发作类型。（2）奥卡西平服药6个月内因不能耐受的不良反应或其他原因停药。（3）用药期间肝肾功能试验异常。（4）研究期间行血液透析或利尿治疗。

3. 一般资料 选择2014年7月–2017年8月在天津市儿童医院神经内科门诊或住院治疗的儿童局灶性癫痫患儿共计110例，男性66例，女性44例；年龄6个月至16岁，中位年龄8（5，11）岁，其中，≤7岁53例，>7岁57例；药物难治性癫痫50例，非药物难治性癫痫60例。

二、研究方法

1. 奥卡西平口服治疗 所有患儿一经明确诊断均予奥卡西平（商品名：曲莱，规格：150 mg/片，瑞士Novartis公司；商品名：曲莱口服液，规格：60 mg/ml，瑞士Novartis公司）单药或添加治疗，初始药物治疗剂量5～10 mg/（kg·d），每周增量1次、每次增量≤10 mg/（kg·d），维持剂量≤60 mg/（kg·d）、2次/d。

2. MHD血药浓度测定 所有患儿均于末次调整奥卡西平剂量后连续规律服药≥3个月，清晨服药前采集外周静脉血1 ml，分离血清，采用高效液相色谱（HPLC）法测定MHD血药谷浓度。（1）药品与试剂：MHD标准品（MHD含量≥98%）由南京康满林化工实业有限公司提供，内标物5-羟基5-乙基巴比妥酸购自美国Sigma公司。（2）仪器：Thermo Scientific Dionex Ultimate 3000高效液相色谱仪（美国Thermo Fisher Scientific公司），配备Chromeleon7工作站。（3）色谱条件：色谱柱Symmtry C18钢柱（4.60 mm×150.00 mm，填料内径5 μm），流动相为乙腈与pH值6.8的磷酸盐缓冲液（体积比36∶64），紫外线波长214 nm，柱温25 ℃。（4）检测方法：取待测血清共计50 μl，加入含20 mg/L 5-羟基5-乙基巴比妥酸的乙腈溶液80 μl，于离心半径5.50 cm、转速12 000 r/min离心5 min，取上清液20 μl，色谱仪进样，峰值即为目的蛋白含量。（5）色谱分离效果：MHD与内标物波峰的保留时间为2.30和4.20 min，

色谱分离理想、峰形良好、分离完全。

3.统计分析方法 采用SPSS 19.0统计软件进行数据处理与分析。呈正态分布的计量资料以均数±标准差($\bar{x} \pm s$)表示，采用两独立样本的t检验；呈非正态分布的计量资料以中位数和四分位数间距[$M(P_{25}, P_{75})$]表示，采用Mann-Whitney U检验。MHD血药谷浓度与奥卡西平治疗剂量的相关性采用Spearman秩相关分析。以$P \leq 0.05$为差异具有统计学意义。

结 果

本组110例患儿奥卡西平治疗剂量为11.76～55.71 mg/(kg·d)，平均(25.52±7.28) mg/(kg·d)；MHD血药谷浓度0.60～23.80 mg/L、中位值7.00(4.95，10.50) mg/L，其中89例(80.91%)<12 mg/L；Spearman秩相关分析显示，MHD血药谷浓度与奥卡西平治疗剂量呈正相关($r_s=0.337$，$P=0.000$)。

根据性别分组，男性奥卡西平治疗剂量11.76～42.00 mg/(kg·d)、平均为(24.91±6.26) mg/(kg·d)，MHD血药谷浓度0.60～20.00 mg/L、中位值为6.85(4.95，10.05) mg/L；女性奥卡西平治疗剂量11.76～55.71 mg/(kg·d)、平均(26.42±8.58) mg/(kg·d)，MHD血药谷浓度1.80～23.80 mg/L、中位值为7.52(4.58，10.93) mg/L；不同性别患儿奥卡西平治疗剂量和MHD血药谷浓度差异未达到统计学意义(均$P>0.05$，表1)。根据年龄分组，年幼(≤7岁)患儿奥卡西平治疗剂量为11.76～55.71 mg/(kg·d)、平均为(28.09±8.06) mg/(kg·d)，MHD血药谷浓度为0.60～23.80 mg/L、中位值为7.80(5.40，9.50) mg/L；年长(>7岁)患儿奥卡西平的治疗剂量为12.96～36.36 mg/(kg·d)、平均(23.13±5.56) mg/(kg·d)，MHD血药谷浓度为2.10～20.00 mg/L、中位值为6.80(4.55，10.80) mg/L；年长患儿奥卡西平治疗剂量低于年幼患儿且差异有统计学意义($P=0.000$)，而不同性别患儿MHD血药谷浓度差异无统计学意义($P>0.05$，表2)。根据是否为药物难治性癫痫分组，药物难治性癫痫患儿奥卡西平治疗剂量为11.76～55.71 mg/(kg·d)、平均(26.59±8.62) mg/(kg·d)，MHD血药谷浓度为0.60～23.80 mg/L、中位值为6.32(3.05，8.58) mg/L；非药物难治性癫痫患儿奥卡西平治疗剂量为13.52～45.45 mg/(kg·d)、平均水平(24.62±5.87) mg/(kg·d)，MHD血药谷浓度1.20～20.00 mg/L、中位值8.30(5.75，10.85) mg/L；药物难治性癫痫患儿MHD血药谷浓度低于非药物难治性癫痫患儿且差异有统计学意义($P=0.017$)，而奥卡西平治疗剂量组间差异无统计学意义($P>0.05$，表3)。根据奥卡西平单药治疗或药物联合治疗分组，奥卡西平单药治疗44例(40%)，治疗剂量为13.85～45.45 mg/(kg·d)、平均(24.11±5.86) mg/(kg·d)，MHD血药谷浓度为1.20～20.00 mg/L、中位值为8.27(4.80，12.08) mg/L；奥卡西平联合其他抗癫痫药物治疗66例(60%)，奥卡西平治疗剂量为11.76～55.71 mg/(kg·d)、平均(26.46±8.00) mg/(kg·d)，MHD血药谷浓度为0.60～23.80 mg/L、中位值6.80(5.08，9.35) mg/L；单药治疗与药物联合治疗患儿奥卡西平治疗剂量和MHD血药谷浓度差异均无统计学意义(均$P>0.05$，表4)。

讨 论

癫痫的治疗应综合考虑癫痫诊断、分型、病因和药物等因素，首选抗癫痫药物治疗。近年来，以奥卡西平为代表的新型抗癫痫药物显示出优于传统抗癫痫药物的疗效以及更显著的安全性和耐受性。药代动力学是评价抗癫痫药物疗效的基础，最佳的药物代谢模型是线性药代动力学代谢，有利于评价药物疗效和不良反应与药物剂量的关系。本组患儿MHD血药谷浓度与奥卡西平治疗剂量呈正相关关系，但线性关系并不显著($r_s=0.337$，$P=0.000$)，个体差异明显，因此，无法简单地通过奥卡西平治疗剂量判断其MHD血药浓度，应进行实际测定。采用HPLC法测定MHD血药浓度，精密、准确、特异性高，提取过程简单、快速，采血量少，更适用于儿科临床血药浓度监测和药物应用研究[2,10]。临床学者尝试建立儿童癫痫患者奥卡西平药代动力学模型，希望能够通过最少1个时间点的血药浓度测定精确估算个体药代动力学参数，并指导个体化药物治疗方案[11-13]，目前中国已有拟合度良好的模型初步应用于临床[14-16]。

目前，国际上尚无公认的MHD有效血药浓度的参考值范围，本研究采纳的MHD血药浓度正常参考值为12～36 mg/L，89例(80.91%)低于这一参考值范围。我国儿童癫痫患者奥卡西平药代动力学代谢研究中，采用HPLC法测定的MHD血药浓度普遍较低。马婧等[17]纳入987例儿童癫痫患者，采纳的MHD血药浓度正常参考值为15～35 mg/L，452例(45.80%)低于这一参考值范围，且MHD血药浓度

表1 不同性别患儿奥卡西平治疗剂量和MHD血药谷浓度的比较($\bar{x} \pm s$)

Table 1. Comparison of the dose of OXC and the valley point concentration of MHD between children with different sexes ($\bar{x} \pm s$)

Group	N	OXC dose [mg/(kg·d)]	MHD concentration (mg/L)
Male	66	24.91 ± 6.26	6.85 (4.95, 10.05)
Female	44	26.42 ± 8.58	7.52 (4.58, 10.93)
t or *Z* value		1.067	0.604
P value		0.288	0.546

Two-independent-sample *t* test for comparison of OXC dose, and Mann-Whitney *U* test for comparison of MHD concentration。OXC, oxcarbazepine, 奥卡西平; MHD, 10-monohydroxy carbamazepine, 10-单羟基卡马西平

表2 不同年龄患儿奥卡西平治疗剂量和MHD血药谷浓度的比较($\bar{x} \pm s$)

Table 2. Comparison of the dose of OXC and the valley point concentration of MHD in children of different age groups ($\bar{x} \pm s$)

Group	N	OXC dose [mg/(kg·d)]	MHD concentration (mg/L)
≤ 7 years	53	28.09 ± 8.06	7.80 (5.40, 9.50)
> 7 years	57	23.13 ± 5.56	6.80 (4.55, 10.80)
t or *Z* value		3.778	0.179
P value		0.000	0.858

Two-independent-sample *t* test for comparison of OXC dose, and Mann-Whitney *U* test for comparison of MHD concentration。OXC, oxcarbazepine, 奥卡西平; MHD, 10-monohydroxy carbamazepine, 10-单羟基卡马西平

表3 药物难治性癫痫患儿与非药物难治性癫痫患儿奥卡西平治疗剂量和MHD血药谷浓度的比较($\bar{x} \pm s$)

Table 3. Comparison of the dose of OXC and the valley point concentration of MHD between DRE and non-DRE children ($\bar{x} \pm s$)

Group	N	OXC dose [mg/(kg·d)]	MHD concentration (mg/L)
DRE	50	26.59 ± 8.62	6.32 (3.05, 8.58)
Non-DRE	60	24.62 ± 5.87	8.30 (5.75, 10.85)
t or *Z* value		1.417	2.380
P value		0.159	0.017

Two-independent-sample *t* test for comparison of OXC dose, and Mann-Whitney *U* test for comparison of MHD concentration。OXC, oxcarbazepine, 奥卡西平; MHD, 10-monohydroxy carbamazepine, 10-单羟基卡马西平; DRE, drug resistant epilepsy, 药物难治性癫痫

表4 单药治疗患儿与药物联合治疗患儿奥卡西平治疗剂量和MHD血药谷浓度的比较($\bar{x} \pm s$)

Table 4. Comparison of the dose of OXC and the valley point concentration of MHD in children with treatment of single drug versus combined drugs ($\bar{x} \pm s$)

Group	N	OXC dose [mg/(kg·d)]	MHD concentration (mg/L)
Single	44	24.11 ± 5.86	8.27 (4.80, 12.08)
Combined	66	26.46 ± 8.00	6.80 (5.08, 9.35)
t or *Z* value		1.671	1.583
P value		0.098	0.113

Two-independent-sample *t* test for comparison of OXC dose, and Mann-Whitney *U* test for comparison of MHD concentration。OXC, oxcarbazepine, 奥卡西平; MHD, 10-monohydroxy carbamazepine, 10-单羟基卡马西平

随年龄的减小而显著下降。本研究年长(>7岁)患儿奥卡西平治疗剂量低于年幼(≤7岁)患儿,而MHD血药谷浓度组间差异无统计学意义,因此,为获得相同的MHD血药浓度,年幼患儿应服用更大剂量的奥卡西平。汪洋等[5]的研究显示,MHD稳态血药谷浓度>8 mg/L即可获得满意疗效,并根据治疗有效组计算MHD有效血药浓度正常参考值为5~20 mg/L,因此认为,应重新修订中国儿童MHD有效血药浓度正常参考值。本研究未发现奥卡西平联合其他抗癫痫药物治疗对MHD血药谷浓度产生影响,这是由于未区分药物联合治疗的种类和数量,尚待更精确的临床研究。

多项研究探讨MHD血药浓度与临床疗效的关系,结果显示,MHD血药谷浓度与临床疗效呈正相关关系,即在奥卡西平治疗剂量内增加药物剂量可以提高临床疗效[5,10]。在本研究中,药物难治性癫痫和非药物难治性癫痫患儿奥卡西平治疗剂量均于有效范围内,但前者MHD血药谷浓度低于后者且差异有统计学意义。因此,对于儿童药物难治性局灶性癫痫,临床医师在积极寻找致痫灶的同时,还应注意药物代谢因素的影响,监测血药浓度,及时调整药物剂量,避免人为因素导致药物剂量不足。本研究比较药物难治性癫痫患儿与非药物难治性癫痫患儿MHD血药谷浓度时,排除性别、年龄、药物治疗剂量和药物联合治疗的差异,尚待进一步寻找其他药物代谢影响因素。相关临床研究显示,癫痫患者细胞色素P450(*CYP450*)2C19*2或*CYP3A4/5*基因型变异与MHD血药浓度并无关联性[18-19];而Lu等[20]于2017年发现,癫痫患者*UGT1A9*基因多态性可以影响MHD血药浓度和临床疗效,*UGT1A9*基因是人类尿苷二磷酸葡萄糖醛酸基转移酶(UGT)相关基因之一,后者与多种药物代谢有关。由此可见,奥卡西平药代动力学在分子生物学水平的影响因素将成为今后的研究方向。

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