

丙戊酸在治疗儿童癫痫中的安全性研究现况

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摘 要

丙戊酸作为一种经典的广谱抗癫痫药, 具有多种抗癫痫机制, 被广泛的用于治疗几乎所有类型的癫痫及癫痫综合征。尽管大量的研究已证明丙戊酸具有良好的安全性, 但因儿童群体有着不同于成人的生理及药物代谢特点, 一些药物不良反应, 特别是与年龄相关的药物不良反应仍限制了其应用。因此, 本文围绕丙戊酸的药理作用、药代动力学、儿童药物代谢特点以及成人与儿童药物不良反应的异同来对丙戊酸在治疗儿童癫痫中的安全性作出综述。

关键词

丙戊酸, 儿童癫痫, 安全性

Safety of Valproic Acid in the Treatment of Children with Epilepsy

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Abstract

Valproic acid (VPA), as a broad-spectrum antiepileptic drug, is widely used in the treatment of almost all types of seizure, epilepsy and epilepsy syndrome due to its multiple mechanisms of action. Although numerous studies suggest the acceptable safety profile of VPA, some adverse drug

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reactions, especially those age-dependent, limit its application in children as the physiological and drug metabolism characteristics of children are different from adults. Herein, this article reviews the safety of VPA in the treatment of childhood by focusing on its action mechanisms, pharmacokinetics, characteristics of drug metabolism in children and similarities and differences of adverse drug reactions in adults and children.

Keywords

Valproic Acid, Epilepsy of Children, Safety

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1. 引言

癫痫是以持续存在发生痫性发作的倾向, 并因此产生神经、认知、精神及社会上的影响为特征的脑部功能紊乱性疾病[1]。癫痫是神经系统常见慢性疾病, 在全世界范围约有七千万人患癫痫[2]。相较于成人, 儿童拥有更高的患病率, 约为 4%~9%, 并且在逐年增加[3]。儿童期为神经系统发育的关键时期, 在此期易受各种不良因素的影响, 而未经控制的癫痫反复发作则是影响儿童正常神经行为发育的重要不良因素[4] [5]。因此, 癫痫的有效治疗十分关键。目前抗癫痫药物(Antiepileptic drugs, AEDs)仍是儿童癫痫治疗的主要方法, 并且大部分儿童通过单药治疗就可获得长时间的控制[6]。丙戊酸(Valproic acid, VPA)自 50 年前偶然发现其具有抗癫痫作用后, 就成为了抗癫痫治疗的一线药物, 并且由于其拥有多种抗癫痫机制, 已被广泛用于治疗几乎儿童所有类型癫痫及癫痫综合征, 并在某些特殊类型的癫痫及癫痫综合征中有着优于其他 AEDs 的疗效[7]。尽管随着研究的深入, 越来越多的证据表明了 VPA 的安全性, 但在儿童这一特殊群体, 特别是两岁以下儿童中, 一些严重药物不良反应(Adverse drug reactions, ADRs), 诸如严重肝功能损伤(发生率 1/600~1/800)、急性胰腺炎(发生率 < 2%)等, 限制了其应用[8] [9]。因此, 本文旨在总结丙戊酸在治疗儿童癫痫中的安全性, 以此为临床实践中癫痫儿童选择丙戊酸治疗提供一定参考。

2. 丙戊酸的药理作用

经过了近 50 年的研究, VPA 的确切药理机制仍不十分清楚, 但目前认为主要通过以下几种机制发挥抗癫痫作用: 1) 同时通过作用于突触前及突触后两个层面来增强 γ -氨基丁酸(γ -aminobutyric acid, GABA)的抑制活性。除影响 GABA 能神经活动外, 它还可通过调节 N-甲基-D-天冬氨酸受体的表达, 促进大脑皮质可塑性来控制神经兴奋毒性及凋亡[10]; 2) 作用于离子通道发挥效应: 它能调节钠通道、钙通道及钾通道的活性[11]; 3) 除直接调节神经传递通路外, VPA 还具有长期作用。VPA 可通过抑制组蛋白去乙酰化(HDAC)及调节脑源性神经营养因子来调节一些突触受体及信号分子的转录及表达, 这对兴奋毒性及神经保护作用有重要影响[12] [13]。

3. 丙戊酸的药代动力学

VPA 目前在我国临床上常用的剂型包括片剂(普通片和缓释片)、口服液及注射液。对于儿童, 我国主要为口服给药, 应在标准体重范围内按公斤体重计算每日给药剂量, 通常起始量为 15 mg/(Kg·d), 逐渐

增加至维持量 20~30 mg/(Kg·d) [14]。VPA 口服可完全吸收, 并且长期维持治疗中, 其吸收速度较单次给药更快, 其生物利用度高、稳定, 可达 96%~100% [7]。VPA 经吸收后与血浆中白蛋白高度结合, 并与血药浓度呈正相关。当血药浓度 > 50 mg/L 时, 其与血浆白蛋白结合基本饱和, 血浆中未结合态 VPA 浓度将增加[15]。在体内 VPA 绝大部分经肝脏代谢, 仅少数以原型从尿液中排出[16]。在肝脏中 VPA 主要通过 3 种途径代谢: 1) 在二磷酸尿苷葡萄糖苷转移酶(UGT)及其同工酶的催化下完成葡萄糖醛酸化; 2) 在线粒体中完成 β -氧化; 3) 在细胞色素 P450 (CYP)介导下的氧化; 前两种途径占 90% [17]。

4. 儿童药物代谢特点

儿童不是成人的简单缩小, 其各脏器功能不完善, 并处于动态发育的过程中, 而这种特点一定程度影响着药物在儿童体内的反应[18]。新生儿胃内 pH 偏高, 在 2 岁时逐步达到成人水平, 并且相对于成人, 儿童的胃排空速度较慢, 肠蠕动速度较慢, 导致药物在胃肠道停留时间延长, 这些因素都影响着儿童药物的吸收[19]。并且儿童身体的组成成分也随年龄增长而变化, 新生儿和小婴儿的细胞外液及总含水量较成年人高, 这对药物在体内的分布有一定的影响。同时, 新生儿和小婴儿血浆中白蛋白含量及白蛋白与药物的亲和力相对较低, 使得在相同血药浓度下, 血浆中未结合形态药物含量相对偏高[19]。药物的生物转化, 即代谢, 通常在多种代谢酶催化下, 于肝脏内进行。前文所述的代谢酶, 如 UGT 同工酶(UGT1A4、UGT1A6、UGT2B17)、CYP450 超家族在儿童体内活性相对较低, 随着年龄的增加而逐步发育成熟[20]。肾功能的成熟也是一个动态的过程。儿童的肾小球滤过率相对较低, 肾小管分泌功能不成熟, 影响着药物自尿液中排泄[19]。

5. 丙戊酸在儿童癫痫中的应用

VPA 因其有着几乎最广谱的抗癫痫作用, 目前在如全面性癫痫发作、儿童失神性癫痫、青少年肌阵挛性癫痫等儿童常见癫痫类型/癫痫综合征的治疗中均为一线药物[21] [22]。在一些难治性癫痫, 如 Lennox-Gastaut 综合征、Dravet 综合征的治疗中, VPA 也有着难以替代的作用[23] [24]。在儿童癫痫持续状态的治疗中, 当一线药物苯二氮卓类药物无效时, VPA 常作为二线用药, 其疗效与其他二线药物相当, 但起效更快, 不良事件更少[25] [26]。

6. 丙戊酸的不良反应

6.1. 丙戊酸与消化系统不良反应

肝功能损害是 VPA 关于消化系统最常见的不良反应, 主要包括两种类型, 一种相对常见, 主要为轻度转氨酶升高, 而无其他临床症状出现[27]。另一种为相对少见, 但更严重, 甚至可危及生命的急性肝功能衰竭, 发病呈明显年龄相关性。在成人中发生率约为 1/20000, 而在 2 岁以下儿童中发生率明显升高, 发生率在 1/600~1/800 [28], 推测可能与儿童肝内各种代谢酶功能尚未发育成熟相关[20]。其发生的危险因素包括与其他 AEDs 联合治疗、共患某些代谢性疾病及线粒体病(如 leigh 综合征、线粒体脑病乳酸中毒等)。其警报症状包括: 精神状态改变、厌食、呕吐、黄疸等[7]。另一种严重的、可能致死的消化系统不良反应为急性胰腺炎。虽其发生在儿童群体的病例罕见, 但与成人相比, 由药物诱发的病例所占比例更大。而 VPA 是引起儿童药物性急性胰腺炎最常见的药物之一。有研究报道 VPA 诱发的急性胰腺炎儿童病例数多于成人, 尽管没有统计学差异[29] [30]。此外, 一些胃肠道反应, 如胃烧灼感、恶心、呕吐、腹泻等, 也是 VPA 治疗的常见不良反应。虽后果不严重, 但可能影响药物的吸收及患儿服药依从性[31]。值得注意的是, 使用 VPA 治疗的癫痫患儿若出现急性腹痛、腹胀或呕吐等症状, 应排除是否并发急性胰腺炎。

6.2. 丙戊酸与神经及精神系统不良反应。

据既往研究报道, 使用 VPA 治疗癫痫出现神经与精神系统不良反应的概率分别为 14% 和 16% [32]。在儿童患者中常见的临床表现包括: 疲劳、烦躁、嗜睡、注意力下降/缺陷、多动、震颤、性格改变等[33] [34] [35]。而在成年患者中, 眩晕、记忆力下降、眼球震颤相对常见, 通常这些不良反应在调整 VPA 剂量后可缓解[36]。

6.3. 丙戊酸与代谢及内分泌系统不良反应。

VPA 可致癫痫患者血氨升高, 多数患者为无症状性, 少数患者可出现嗜睡、昏睡、昏迷及癫痫发作加重等表现。Yamamoto 等[37]观察到年龄 < 3 岁是高氨血症的危险因素, 并且随着患儿年龄的增长, 患儿血氨浓度升高的程度逐渐降低。体重增加及身体质量指数(Body Mass Index, BMI)增加也是 VPA 治疗中关于代谢功能的常见不良反应[38]。在儿童患者中, VPA 治疗 3 月后即可观察到体重增加, 而在成人患者中这一时间需要 8 月。此外, 在大龄儿童中, 随着 VPA 治疗的时间的延长, 体重又会再次出现下降趋势。相较于成人, 通过饮食疗法及适当锻炼, 儿童的体重增长更易受控制[36]。

高胰岛素血症、胰岛素抵抗及高脂血症也可见于使用 VPA 治疗的癫痫患儿中, 并且这些不良反应推测是 VPA 导致体重增长的机制[8]。长期使用 VPA 还可干扰下丘脑 - 垂体 - 性腺轴的正常功能, 引起高雄激素血症, 并可与高胰岛素血症、胰岛素抵抗等协同作用, 引起女性患者月经紊乱、多囊卵巢综合征甚至不孕。而在男性患者中, 则表现为精子活力下降、睾丸体积减少及不育[7]。近年来的研究还发现, VPA 对骨骼代谢也有一定的影响, 表现为患者腰椎及骨骼颈的骨密度降低。在儿童患者中, 还可观察血清 25-羟基 - 维生素 D3 水平降低及甲状旁腺激素水平升高[39]。

6.4. 丙戊酸与血液系统不良反应。

在过去的研究中, 已有多种血液系统异常被报道与使用 VPA 治疗癫痫有关, 这些异常通常在围术期检查时被发现。VPA 可同时影响凝血系统及抗凝血系统, 可能导致凝血因子VII、凝血因子VIII及纤维蛋白原水平下降[40]。一项大型队列研究发现在接受 VPA 治疗的癫痫儿童中, 显著的凝血功能障碍发生率约为 4% [41]。另有研究表明, 长期使用 VPA 还可以引起血小板减少、白细胞减少及三系下降[42], 其中血小板减低的发生率与 VPA 的血药浓度呈正相关[40]。也有个案报道显示 VPA 具有骨髓毒性, 可导致再生障碍性贫血[43]。

7. 总结

自 50 多年前, VPA 被批准用于临床治疗癫痫以来, 已有许多实验证明了 VPA 具有最广泛的作用机制以及最广谱的抗癫痫活性, 其疗效及安全性已经过充分证实。但儿童由于其器官功能的不成熟性及生长发育性, VPA 在其代谢特点并不与成人相同, 因此 VPA 药物不良反应发生的类型以及概率在儿童群体中有自己的特点。致死性肝功能衰竭、急性胰腺炎等危及生命的严重不良反应与年龄密切相关。其危险因素包括大剂量给药、联合用药、共患某些遗传代谢性疾病等。未来的研究重点主要在于探索儿童如何在最安全的情况下发挥 VPA 的最大效能。

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