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三种非典型抗精神病药对儿童青少年精神分裂症患者血脂、 肝功能和认知功能的影响*

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摘要 目的:探讨利培酮、阿立哌唑、奥氮平分别对儿童青少年精神分裂症患者肝功能、血脂和认知功能的影响。**方法:**选取 2015 年 1 月至 2019 年 12 月我院收治的 84 例儿童青少年精神分裂症患者,采用乱数表法随机分为阿立哌唑组($n=28$,阿立哌唑治疗)、利培酮组($n=28$,利培酮治疗)、奥氮平组($n=28$,奥氮平治疗),均治疗 8 周,对比三组患者症状评分、血脂、肝功能、认知功能以及不良反应。**结果:**三组治疗 8 周后阳性与阴性症状量表(PANSS)评分整体比较无差异($P>0.05$),三组治疗 8 周后 PANSS 评分均较治疗前降低($P<0.05$)。奥氮平组、利培酮组治疗 8 周后三酰甘油(TG)、总胆固醇(TC)、低密度脂蛋白(LDL-C)高于阿立哌唑组,且奥氮平组高于利培酮组($P<0.05$);奥氮平组、利培酮组治疗 8 周后高密度脂蛋白(HDL-C)低于阿立哌唑组,且奥氮平组低于利培酮组($P<0.05$)。三组不良反应发生率整体比较无差异($P>0.05$)。阿立哌唑组治疗 8 周后延迟回忆数、即刻回忆数、回忆总数、再认数评分均高于利培酮组、奥氮平组($P<0.05$)。利培酮组治疗 8 周后 ALT、AST、TBIL 高于治疗前($P<0.05$),利培酮组治疗 8 周后 ALT、AST、TBIL 高于阿立哌唑组、奥氮平组($P<0.05$)。**结论:**利培酮、阿立哌唑、奥氮平应用于儿童青少年精神分裂症中,可获得相当的治疗效果,其中利培酮对肝功能影响较大,奥氮平对人体血脂影响较大,阿立哌唑对血脂、肝功能影响轻,改善认知功能效果优于利培酮、奥氮平。

关键词:阿立哌唑;利培酮;奥氮平;儿童青少年;精神分裂症;血脂;肝功能;认知功能

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Effects of Three Atypical Antipsychotics on Blood Lipid, Liver Function and Cognitive Function in Children and Adolescents with Schizophrenia*

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ABSTRACT Objective: To investigate the effects of risperidone, aripiprazole and olanzapine on liver function, blood lipid and cognitive function in children and adolescents with schizophrenia. **Methods:** 84 cases of children and adolescents with schizophrenia who were admitted to our hospital from January 2015 to December 2019 were selected. They were randomly divided into aripiprazole group ($n=28$, aripiprazole treatment), risperidone group ($n=28$, risperidone treatment), olanzapine group ($n=28$, olanzapine treatment) by randomly number table method. All patients were treated for 8 weeks. Symptom score, blood lipid, liver function, cognitive function and adverse reactions of the three groups were compared. **Results:** There was no significant difference in positive and negative symptoms scale (PANSS) scores among the three groups at 8 weeks after treatment ($P>0.05$), 8 weeks after treatment, the scores of PANSS in the three groups were lower than those before treatment ($P<0.05$), but The levels of triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL-C) in olanzapine group and risperidone group at 8 weeks after treatment were higher than those in aripiprazole group, and those in olanzapine group were higher than those in risperidone group ($P<0.05$). The high density lipoprotein (HDL-C) in olanzapine group and risperidone group at 8 weeks after treatment was lower than that in aripiprazole group, and that in olanzapine group was lower than that in risperidone group ($P<0.05$). There was no significant difference in the incidence rate of adverse reactions among the three groups ($P>0.05$). 8 weeks after treatment, the scores of delayed recall, immediate recall, total recall and recognition number in aripiprazole group were higher than those in risperidone group and olanzapine group ($P<0.05$). 8 weeks after treatment, ALT, AST and TBIL in risperidone group were higher than those before treatment ($P<0.05$), while ALT, AST and TBIL in risperidone group at 8 weeks after treatment were higher than those in aripiprazole group and olanzapine groups ($P<0.05$). **Conclusion:** Risperidone, aripiprazole and

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olanzapine are used in children and adolescents with schizophrenia, they can obtain considerable therapeutic effect. Among them, risperidone has a greater impact on liver function, olanzapine has a greater impact on blood lipid. Aripiprazole has less effect on blood lipid and liver function, and the effect of improving cognitive function is better than risperidone and olanzapine.

Key words: Aripiprazole; Risperidone; Olanzapine; Children and adolescents; Schizophrenia; Blood lipid; Liver function; Cognitive function

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前言

精神分裂症是精神病中最常见的一种精神病,临床表现为阳性与阴性症状、社会功能减退及认知功能障碍^[1,2]。近年来相关数据显示^[3],儿童青少年精神分裂症发病率约为 0.5%,且呈增长趋势。目前非典型抗精神病药是儿童青少年精神分裂症患者的一线用药方案,但用药后对机体糖脂代谢的影响也逐渐引起广大临床工作者的重视^[4-6]。若糖脂代谢分泌紊乱的话,将引起机体一系列机能变化,降低患者的生活质量^[7]。阿立哌唑、利培酮、奥氮平是临床常见的非典型抗精神病药,现有关上述药物对儿童青少年精神分裂症患者的血脂、肝功能和认知功能的影响的综合报道尚不多见。本研究就此展开比较了三种药物的治疗效果,以期为指导临床医生安全用药提供数据支持。

1 资料与方法

1.1 一般资料

选取 2015 年 1 月至 2019 年 12 月我院收治的儿童青少年精神分裂症患者 84 例,纳入标准:(1)年龄 10~18 岁;(2)符合美国精神病诊断与统计手册(DSM-IV)(第 4 版)精神分裂症诊断标准^[8];(3)首次发病,病程≤60 个月;(4)患者家属知情本次研究且签署了同意书;(5)入组前未曾服用任何抗精神病药物。排除标准:(1)入组前使用引起糖脂代谢异常的药物;(2)物质及酒精滥用及对本次研究药物过敏者;(3)合并严重躯体疾病和神经系统疾病者;(4)具有明显暴力或自伤自杀倾向者;(5)有癫痫病史者;(6)有糖尿病和高脂血症者。采用乱数表法随机分为阿立哌唑组(n=28)、利培酮组(n=28)、奥氮平组(n=28),三组患者中因各种原因脱落 4 例,其中阿立哌唑组 2 例、利培酮组 1 例、奥氮平组 1 例,实际共完成 80 例。其中阿立哌唑组男 15 例,女 11 例,年龄 10~18 岁,平均(15.09±1.33)岁;病程 6~60 月,平均(38.92±7.76)月;利培酮组男 16 例,女 11 例,年龄 12~18 岁,平均(14.83±1.52)岁;病程 8~60 月,平均(38.24±9.42)月;奥氮平组男 14 例,女 13 例,年龄 11~17 岁,平均(14.62±1.18)岁;病程 10~59 月,平均(37.69±10.42)月。三组一般资料对比无差异($P>0.05$),具有可比性。本次研究已通过我院伦理学委员会批准进行。

1.2 方法

三组治疗药物均从小剂量开始,7 d 内调整至有效治疗剂量。三组患者用药方案具体如下:阿立哌唑(国药准字 H20041507,上海上药中西制药有限公司,规格:10 mg),10~20 mg/d;奥氮平(国药准字 H20010799,江苏豪森药业集团有限公司,规格:10 mg/10~20 mg/d。利培酮(国药准字 H20050042,齐鲁制药有限公司,规格:3 mg),2 mg/d。三组均治

疗 8 周。

1.3 观察指标

(1)临床疗效评价于治疗前、治疗 8 周后采用阳性与阴性症状量表(PANSS)^[9]进行,PANSS 包括阴性症状(7 条目)、阳性症状(7 条目)、一般病理症状(16 条目),分值越高则症状越重。(2)评定药物安全性:统计治疗期间不良反应。(3)于治疗前、治疗 8 周后采用霍普金斯词汇学习测验一修订版(HVLT-R)^[10]评价患者认知功能,其中 HVLT-R 评价指标包括延迟回忆数、即刻回忆数、回忆总数及再认数,患者得分越高表示认知功能越好。(4)抽取患者治疗前、治疗 8 周后空腹血液标本 5 mL,采用湘仪 TDZ-W8 离心机(转速 4000 r/min,离心半径 16 cm)离心 10 min,分离血清后置于冰箱中待测。采用全自动生化分析仪(贝克曼 DXC800)测定患者三酰甘油(TG)、高密度脂蛋白(HDL-C)、总胆固醇(TC)、低密度脂蛋白(LDL-C)及肝功能指标:谷丙转氨酶(ALT)、谷草转氨酶(AST)、以及总胆红素(TBIL)。

1.4 统计学方法

SPSS 25.0 进行数据分析,计量资料均符合正态分布,以($\bar{x}\pm s$)表示,两组数据比较采用 t 检验,多组数据比较采用 F 检验。以百分率表示计数资料采用 χ^2 检验。所有统计均采用双侧检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 三组 PANSS 评分对比

阿立哌唑组治疗前 PANSS 评分为(72.24±6.74)分,治疗 8 周后为(39.35±5.46)分;利培酮组治疗前 PANSS 评分为(72.41±7.69)分,治疗 8 周后为(39.69±4.51)分;奥氮平组治疗前 PANSS 评分为(72.12±6.95)分,治疗 8 周后为(39.78±5.21)分;三组治疗 8 周后 PANSS 评分均较治疗前降低($P<0.05$),三组治疗 8 周后 PANSS 评分比较无差异($P>0.05$)。

2.2 三组血脂指标对比

三组治疗前 TC、TG、LDL-C、HDL-C 整体比较差异无统计学意义($P>0.05$),阿立哌唑组治疗前、治疗 8 周后 TC、TG、LDL-C、HDL-C 组内比较差异无统计学意义($P>0.05$),利培酮组、奥氮平组治疗 8 周后 TC、TG、LDL-C 较治疗前升高,HDL-C 较治疗前降低($P<0.05$),奥氮平组、利培酮组治疗 8 周后 TC、TG、LDL-C 高于阿立哌唑组,且奥氮平组高于利培酮组($P<0.05$),奥氮平组、利培酮组治疗 8 周后 HDL-C 低于阿立哌唑组,且奥氮平组低于利培酮组($P<0.05$),详见表 1。

2.3 三组认知功能对比

三组治疗前延迟回忆数、即刻回忆数、回忆总数、再认数评分整体比较差异无统计学意义($P>0.05$),三组治疗 8 周后延迟回忆数、即刻回忆数、回忆总数、再认数评分较治疗前升高

($P<0.05$),阿立哌唑组治疗 8 周后延迟回忆数、即刻回忆数、回忆总数、再认数评分均高于利培酮组、奥氮平组($P<0.05$),利培酮组、奥氮平组延迟回忆数、即刻回忆数、回忆总数、再认数评分组间比较差异无统计学意义($P>0.05$),如表 2 所示。

表 1 三组血脂指标对比($\bar{x}\pm s$,mmol/L)

Table 1 Comparison of blood lipid indexes among three groups($\bar{x}\pm s$, mmol/L)

Groups	Time points	TC	TG	LDL-C	HDL-C
Aripiprazole group(n=26)	Before treatment	3.72±0.28	1.38±0.24	2.67±0.23	1.29±0.25
	8 weeks after treatment	3.75±0.25	1.41±0.19	2.69±0.21	1.26±0.26
Risperidone group(n=27)	Before treatment	3.74±0.22	1.36±0.18	2.64±0.21	1.31±0.17
	8 weeks after treatment	3.95±0.24 ^{ac}	1.56±0.15 ^{ac}	2.93±0.23 ^{ac}	1.02±0.13 ^{ac}
Olanzapine group(n=27)	Before treatment	3.75±0.22	1.39±0.24	2.64±0.22	1.32±0.19
	8 weeks after treatment	4.32±0.23 ^{abc}	1.84±0.29 ^{abc}	3.29±0.26 ^{abc}	0.87±0.12 ^{abc}

Note: compared with before treatment, ^a $P<0.05$; compared with risperidone group, ^b $P<0.05$; compared with aripiprazole group, ^c $P<0.05$.

表 2 三组认知功能对比($\bar{x}\pm s$,分)

Table 2 Comparison of cognitive function among three groups($\bar{x}\pm s$, score)

Groups	Time points	Delayed recall number	Immediate recall	Total recall	Recognition number
Aripiprazole group(n=26)	Before treatment	8.13±0.58	22.97±3.54	30.23±4.68	10.41±1.59
	8 weeks after treatment	12.64±1.76 ^a	29.05±4.32 ^a	38.04±4.16 ^a	17.24±2.18 ^a
Risperidone group(n=27)	Before treatment	8.16±0.55	22.64±3.65	30.35±3.09	10.34±1.67
	8 weeks after treatment	10.31±0.95 ^{ac}	25.71±3.28 ^{ac}	34.01±3.03 ^{ac}	13.85±2.57 ^{ac}
Olanzapine group(n=27)	Before treatment	8.14±0.42	22.85±3.95	30.26±4.02	10.29±1.95
	8 weeks after treatment	10.35±1.18 ^{ac}	25.79±3.52 ^{ac}	34.25±4.57 ^{ac}	13.94±2.58 ^{ac}

Note: compared with before treatment, ^a $P<0.05$; compared with aripiprazole group, ^c $P<0.05$.

2.4 三组肝功能情况对比

三组治疗前 ALT、AST、TBIL 对比差异无统计学意义($P>0.05$),阿立哌唑组、奥氮平组治疗 8 周后 ALT、AST、TBIL 与治疗前对比差异无统计学意义($P>0.05$),利培酮组治疗 8 周

后 ALT、AST、TBIL 高于治疗前($P<0.05$),利培酮组治疗 8 周后 ALT、AST、TBIL 高于阿立哌唑组、奥氮平组($P<0.05$),详见表 3。

表 3 三组肝功能情况对比($\bar{x}\pm s$)

Table 3 Comparison of liver function among three groups($\bar{x}\pm s$)

Groups	Time points	ALT(U/L)	AST(U/L)	TBIL(μ mol/L)
Aripiprazole group(n=26)	Before treatment	22.64±2.33	18.96±2.13	13.90±2.78
	8 weeks after treatment	22.98±2.47	19.32±2.28	14.23±2.16
Risperidone group(n=27)	Before treatment	22.65±2.29	18.63±2.49	13.28±2.48
	8 weeks after treatment	27.92±2.32	27.32±2.82	21.34±3.51
Olanzapine group(n=27)	Before treatment	22.85±2.43	18.54±2.64	13.57±2.35
	8 weeks after treatment	22.93±2.38	19.09±2.93	14.10±3.27

2.5 三组不良反应发生率对比

三组不良反应发生率整体比较差异无统计学意义($P>0.05$),如表 4 所示。

3 讨论

精神分裂症是多因素导致的疾病,涉及感知觉、思维、行为、情感等多方面的障碍,部分患者会出现智力低下、孤立性幻

觉、记忆方面功能障碍及妄想等,加剧家庭及社会的负担^[11-13]。据统计^[14],约有三分之一的精神分裂症患者首次发病年龄在 19 岁以前。现临床针对该病的治疗仍以药物为主,传统抗精神病药物多为中枢多巴胺受体拮抗剂,虽可有效缓解精神分裂症患者的阳性症状,但对于其阴性症状改善效果一般,同时对患者的认知功能几乎无改善作用,反而可加重患者对认知功能的损害^[15-17]。由于儿童青少年身体发育不成熟,耐受性较低,且认知

表 4 三组不良反应发生率对比【例(%)】

Table 4 Comparison of incidence rate of adverse reactions among three groups[n(%)]

Groups	Nausea and vomiting	Dry mouth and sweating	Weight gain	Can't sit still	Total incidence rate
Aripiprazole group(n=26)	2(7.69)	1(3.85)	2(7.69)	2(7.69)	7(26.92)
Risperidone group(n=27)	2(7.41)	1(3.70)	2(7.41)	1(3.70)	6(22.22)
Olanzapine group(n=27)	3(11.11)	1(3.70)	2(7.41)	3(11.11)	9(33.33)
χ^2	-				0.847
P	-				0.426

功能的逐步损害也可让患者无法适应于日常生活及社会活动中,故而传统抗精神病药物在临床的应用逐渐被非典型抗精神病药物所取代^[18]。

近几年,伴随着阿立哌唑、利培酮、奥氮平等非典型抗精神病药在临床中的推广应用,精神分裂症患者的治疗取得了较大进展。国内外不少研究证实^[19,20],精神分裂症患者采用非典型抗精神病药物治疗可明显改善其阳性、阴性症状。本研究三组治疗 8 周后 PANSS 评分均较治疗前降低,且三组整体评分对比无差异,可见阿立哌唑、利培酮、奥氮平可获得相当的治疗效果。阿立哌唑改善阳性症状的机制在于下调亢进的多巴胺 D2 活性,改善阴性症状的机制在于上调低兴奋状态的多巴胺 D2 神经元^[21]。利培酮与多巴胺的平衡拮抗剂可使精神分裂症病人临床表征有效缓解^[22]。奥氮平与 5-HT₂ 受体和多巴胺 D2 受体有较好的亲和力,可有效改善精神分裂症患者的症状^[23],因此三组患者的症状评分均有所改善。然而在临床使用中,该类药物常引起糖脂代谢异常,增加心血管事件发生。目前有关该类药物所致血脂代谢异常的机制尚不明确,既往有学者认为可能是与药物引起的胰岛素抵抗、增加食欲及体重等多种因素有关^[24]。本研究结果显示,阿立哌唑对血脂影响轻,而奥氮平对人体血脂影响最大。可能与不同非典型抗精神病药物对人体不同作用机制的受体亲密度有关,奥氮平具有一定的镇静效果,会减少了患者的活动量,导致脂肪堆积,同时奥氮平还会抑制甲状腺激素分泌进而影响代谢,血脂合成增加,最终导致人体出现一系列不同程度的代谢变化有关^[25]。考虑到儿童青少年时期处于学习的一个阶段,认知功能的恢复对于其改善病情有积极的促进意义。本研究结果发现,阿立哌唑的认知功能改善效果优于利培酮、奥氮平。可能与阿立哌唑是一种具备抗抑郁、抗焦虑,控制激越与敌对行为疗效的药物,可使病人识别能力改善,进而促进认知功能改善^[26,27]。盛承东等学者^[28]的研究发现,阿立哌唑、利培酮、奥氮平均可改善人体认知功能,其中以阿立哌唑的效果更为显著,与本次研究结果基本一致。在服用非典型抗精神病药治疗过程中药物所致的肝功能损害、恶心呕吐、口干发汗、体重上升、静坐不能等均是常见的不良反应,其机理可能与药物代谢过程中的毒性传递有关^[29]。本研究结果显示,利培酮组对人体的肝功能损害稍高于阿立哌唑组、奥氮平组,这可能与药物的作用机制及在体内的代谢途径有关^[30]。

综上所述,利培酮、阿立哌唑、奥氮平应用于儿童青少年精神分裂症中,可获得相当的治疗效果,其中利培酮对肝功能影响较大,奥氮平对人体血脂影响较大,阿立哌唑对血脂、肝功能影响轻,改善认知功能效果优于利培酮、奥氮平。

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