

doi: 10.13241/j.cnki.pmb.2019.14.024

长期吸入布地奈德联合孟鲁司特钠治疗过敏性哮喘基因阳性患儿的临床观察 *

周明琪¹ 耿瑞花^{2Δ} 方素芹² 刘莉³ 王娟³

(1 胜利油田中心医院儿科 山东 东营 257034; 2 东营市垦利区人民医院儿科 山东 东营 257500;

3 泰山医学院附属医院儿科 山东 泰安 271000)

摘要 目的:观察长期吸入布地奈德联合孟鲁司特钠治疗过敏性哮喘基因阳性患儿的临床疗效。**方法:**将 88 例支气管哮喘患儿按简单随机法分为对照组(n=46)和研究组(n=42),两组均予以常规治疗,对照组在常规治疗基础上长期吸入布地奈德治疗,研究组在对照组基础上联合孟鲁司特钠治疗,比较两组临床疗效、症状及体征消失时间,治疗前后嗜酸粒细胞阳离子蛋白(ECP)、嗜酸粒细胞(EOS)计数、免疫球蛋白(IgE)、白介素-4(IL-4)和肺功能的变化及不良反应的发生情况。**结果:**治疗后,研究组总有效率显著高于对照组(97.62% vs. 84.78%, $P<0.05$),气促、哮喘音、肺部啰音、咳嗽消失时间均明显短于对照组($P<0.05$)。治疗前,两组 ECP、EOS、IgE、IL-4 水平、峰值呼气流速(PEF)、第一秒用力呼气容积(FEV1)比较差异无统计学意义($P>0.05$);治疗后,两组 ECP、EOS、IgE 及 IL-4 水平较治疗前下降($P<0.05$),研究组以上指标低于对照组($P<0.05$),两组治疗后 PFE 及 FEV1 较治疗前心脏上升,且研究组以上指标明显高于对照组($P<0.05$)。两组总不良反应发生率比较差异无统计学意义($P>0.05$)。**结论:**长期吸入布地奈德联合孟鲁司特钠可提高过敏性哮喘基因阳性患儿的疗效,显著减轻患儿症状,控制气道炎症反应,改善肺功能。

关键词:过敏性哮喘基因阳性;布地奈德;孟鲁司特钠

中图分类号:R562.25;R725.6 **文献标识码:**A **文章编号:**1673-6273(2019)14-2716-05

Clinical Observation of the Effect of Long-Term Inhalation of Budesonide Combined with Montelukast Sodium on Children with Gene Positive Allergic Asthma*

ZHOU Ming-qi¹, GENG Rui-hua^{2Δ}, FANG Su-qin², LIU Li³, WANG Juan³

(1 Shengli Oilfield Central Hospital, Pediatrics, Shandong, Dongying, 257034, China;

2 Dongying Kenli District People's Hospital, Pediatrics, Shandong, Dongying, 257500, China;

3 Affiliated Hospital of Taishan Medical College, Department of Pediatrics, Shandong, Taian, 271000, China)

ABSTRACT Objective: To observe the clinical effect of long-term inhalation of budesonide combined with montelukast sodium in children with gene positive allergic asthma. **Methods:** 88 cases of children with bronchial asthma according to simple random method were divided into the control group (n=46) and research group (n=42), both groups of conventional treatment, the control group on the basis of routine therapy long-term inhaled budesonide therapy, the research group was treated with montelukast sodium on the basis of the control group, then clinical curative effect, the symptoms and signs disappeared time comparison, acidophilic granulocyte cationic protein (ECP), acidophilic granulocyte (EOS) counting, immunoglobulin (IgE), interleukin 4 (IL-4) and pulmonary function changes before and after the treatment, and adverse reactions occur in both group were compared. **Results:** After treatment, the total effective rate in the research group was higher than that in the control group, and the disappearance time of shortness of breath, wheeze, rumble in lungs and cough was lesser than that in the control group, the difference was statistically significant ($P<0.05$). Before treatment, levels of ECP, EOS, IgE and IL-4, PEF and FEV1 in the two groups were no significant difference ($P>0.05$). After treatment, the levels of ECP, EOS, IgE and IL-4 in both groups were decreased compared with that before treatment, the above indexes in the research group were lower than those in the control group, PFE and FEV1 were higher than those before treatment, and the differences in the research group were statistically significant ($P<0.05$). There was no statistically significant difference in the incidence of total adverse reactions between the two groups ($P>0.05$). **Conclusion:** long-term inhalation of budesonide combined with montelukast sodium can improve the efficacy of children with allergic asthma gene positive, reduce symptoms, control airway inflammation and improve lung function.

Key words: Allergic asthma gene positive; Budesonide; Montelukast sodium

Chinese Library Classification(CLC): R562.25; R725.6 **Document code:** A

Article ID: 1673-6273(2019)14-2716-05

* 基金项目:山东省医药卫生科技发展计划项目(2015WS0131)

作者简介:周明琪(1955-),男,主任医师,电话:13605466869, E-mail:liqian200801@163.com

Δ 通讯作者:耿瑞花(1967-),女,副主任医师,研究方向:呼吸、新生儿疾病, E-mail:13562289776@139.com, 电话:13562289776

(收稿日期:2019-05-08 接受日期:2019-05-31)

前言

支气管哮喘是小儿呼吸道的常见疾病之一,以发作性喘息、哮鸣、咳嗽为主要症状,多夜间加重,容易反复发作,病情严重者容易并发肺心病、呼吸衰竭等并发症,明显影响患儿的身心发育^[1]。支气管哮喘的病因及发病机制尚无明确定论,研究认为可能和过敏原暴露、免疫、环境等因素相关^[1,2]。近年来研究显示^[3,4]目前已知的 β_2 肾上腺素能受体基因(ADRB2)、5脂氧化酶(ALOX5)等基因和支气管哮喘的发生有明显相关性,其阳性表达可能增加气道敏感性及过敏性哮喘的发生风险。吸入糖皮质激素是支气管哮喘的主要抗炎手段,可直接作用于病灶组织,并于短时间内分布于肺泡管、毛细支气管等区域,且以较小剂量起到最大治疗效果^[5]。

布地奈德作为糖皮质激素的代表药物可抑制组胺等过敏活性物质的释放,且可减轻抗原抗体结合时的酶促反应,减轻气道平滑肌的收缩反应,但有研究认为^[6]布地奈德对部分支气管哮喘患儿的疗效不甚理想。孟鲁斯特纳等抗白三烯药物可直接抑制支气管收缩,保持呼吸道通畅,从而减轻哮喘患儿症状,改善肺功能,降低哮喘的恶性风险。相关研究报道^[7]吸入糖皮质激素的同时联合抗白三烯药物可协同增效,减少吸入激素的剂量。尽管目前临床有关布地奈德联合孟鲁司特钠在小儿哮喘中的研究较多,但长期应用的安全性及疗效尚存在争议。本研究主要探讨了长期吸入布地奈德联合孟鲁司特钠治疗过敏性哮喘基因阳性患儿的临床疗效并分析可能的作用机制。

1 资料与方法

1.1 一般资料

选择我院2016年1月~2018年6月收治的88例支气管哮喘患儿,纳入标准:符合支气管哮喘诊断标准^[8]:①年龄>3岁,喘息反复发作;②发作时双肺可见哮鸣音、呼气过长;③支气管舒张剂疗效明显;④除外其他因素所致咳嗽、胸闷、喘息;⑤支气管舒张试验阳性;⑥ADRB2、ALOX5、白三烯C4合成酶(LTC4S)至少一个位点检测结果阳性;⑦为急性发作期;⑧近1个月内未接受糖皮质激素治疗。排除标准:支气管异物、重症肺炎、喉软骨发育不良、支气管肺发育不良等其他呼吸道疾病;心血管、免疫系统疾病;呼吸衰竭等严重并发症;本研究药物禁忌证。

将88例患儿按简单随机法分为对照组(n=46)和研究组(n=42)。对照组中,男26例,女20例;年龄3~12岁,平均(6.12±1.06)岁;病程3个月~5年,平均(2.14±0.48)年;体温(37.15±0.28)℃;白细胞计数(6.12±0.85)×10⁹/L;淋巴细胞计数(2.19±0.51)×10⁹/L;中性粒细胞计数(2.75±0.62)×10⁹/L。研究组中,男24例,女18例;年龄3~12岁,平均(6.29±1.01)岁;

病程6个月~5年,平均(2.16±0.43)年;体温(37.31±0.19)℃;白细胞计数(6.18±0.81)×10⁹/L;淋巴细胞计数(2.23±0.42)×10⁹/L;中性粒细胞计数(2.71±0.55)×10⁹/L。两组患儿基线资料比较差异均无统计学意义(P>0.05),具有可比性。本研究患儿家属均签署知情同意书,且经过医院伦理委员会许可。

1.2 治疗方法

所有患儿均完善体格、胸部X线血清学、病原学、肺功能等检查,并予以解痉平喘、止咳化痰等常规治疗,合并感染者予以抗感染治疗,喘息发作时吸入沙丁胺醇对症治疗。对照组予以吸入布地奈德治疗,将0.5~1.0 mg布地奈德混悬液(厂家:上海信谊百路达药业有限公司,规格:20 mg/瓶,批号:20150812)+1 mL生理盐水雾化吸入,每天2次。待患儿咳嗽消失、体温正常和肺部哮鸣音消失后持续予以吸入小剂量布地奈德治疗3个月,每次0.2 mg,每天2次。研究组在对照组基础上联合孟鲁斯特纳(厂家:四川大冢制药有限公司,规格:4 mg/片,批号:20151021)治疗,3~6岁睡前口服4 mg,6岁以上5 mg,每天1次,持续治疗3个月。于治疗结束时评价疗效,记录患儿症状及体征消失时间,用药期间不良反应的发生情况。

1.3 观察指标

1.3.1 临床疗效 治疗后,很少发生症状,肺功能接近正常,最低限度地接受缓解药物,不因哮喘急诊或者住院,极少发生不良反应为临床控制;症状、体征明显减轻,肺功能接近正常,哮喘发作次数减少为好转;未达到以上标准为无效。临床控制率及好转率为总有效率^[9]。

1.3.2 血液指标 于治疗前及治疗结束时采集患儿空腹外周静脉血4 mL,常规分离血清,用酶联免疫法检测血清嗜酸粒细胞阳离子蛋白(ECP)、免疫球蛋白(IgE)及白介素-4(IL-4)水平。另外将2 mL静脉血抗凝后,用伊红染色,在显微镜下观察嗜酸粒细胞(EOS)计数。

1.3.3 肺通气功能 于治疗前及治疗结束时采用肺功能仪(北京格瑞朗科技发展有限公司)测定峰值呼气流速(PEF)、第一秒用力呼气容积(FEV1)。

1.4 统计学分析

数据处理选用SPSS18.0软件包,计量资料以($\bar{x} \pm s$)表示,组间比较选用t检验,计数资料以[(例)%]表示,组间比较采用 χ^2 检验,以P<0.05表示差异有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后,研究组总有效率为97.62%,显著高于对照组(84.78%),差异有统计学意义(P<0.05),见表1。

表1 两组临床疗效比较[例(%)]

Table 1 Comparison of the clinical efficacy between the two groups [case (%)]

Groups	n	Clinical control	Better	Invalid	Total effective rate
Control group	46	7(15.22)	32(69.57)	7(15.21)	39(84.78)
Research group	42	13(30.95)	28(66.67)	1(2.38)	41(97.62)*

Note: Compared with the control group, *P<0.05.

2.2 两组症状及体征消失时间比较

组,差异有统计学意义($P<0.05$),见表2。

研究组气促、哮鸣音、肺部啰音、咳嗽消失时间均短于对照

表2 两组症状及体征消失时间的比较($\bar{x} \pm s$)

Table 2 Comparison of the disappearance time of symptoms and signs between the two groups($\bar{x} \pm s$)

Groups	n	Shortness of breath	Wheezing	Lung Sound	Cough
Control group	46	3.15 $\pm$ 0.46	5.73 $\pm$ 0.78	6.60 $\pm$ 0.79	7.03 $\pm$ 0.81
Research group	42	2.09 $\pm$ 0.31 [#]	3.81 $\pm$ 0.46 [#]	4.57 $\pm$ 0.51 [#]	5.17 $\pm$ 0.55 [#]

Note: Compared with the control group, [#] $P<0.05$.

2.3 两组治疗前后 ECP、EOS、IgE 及 IL-4 水平比较

显著下降,研究组以上指标均明显低于对照组,差异有统计学意义($P<0.05$),见表3。

治疗前,两组 ECP、EOS、IgE 及 IL-4 水平比较差异无统计学意义($P>0.05$);治疗后,两组 ECP、EOS、IgE 及 IL-4 较治疗前

表3 两组治疗前后 ECP、EOS、IgE 及 IL-4 水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the levels of ECP, EOS, IgE and IL-4 between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Time	ECP(μ g/L)	EOS(%)	IgE(IU/L)	IL-4(μ g/L)
Control group	46	Before treatment	38.11 $\pm$ 4.15	0.18 $\pm$ 0.03	101.07 $\pm$ 10.28	28.81 $\pm$ 3.85
		After treatment	20.07 $\pm$ 3.40 ^a	0.10 $\pm$ 0.01 ^a	60.26 $\pm$ 7.59 ^a	12.29 $\pm$ 1.29 ^a
Research group	42	Before treatment	36.30 $\pm$ 4.86	0.19 $\pm$ 0.02	98.45 $\pm$ 12.51	30.27 $\pm$ 3.20
		After treatment	14.20 $\pm$ 2.11 ^{a #}	0.07 $\pm$ 0.01 ^{a #}	44.20 $\pm$ 5.86 ^{a #}	8.85 $\pm$ 1.12 ^{a #}

Note: Compared with the control group, [#] $P<0.05$; Compared with the same group before treatment, ^a $P<0.05$.

2.5 两组治疗前后肺通气功能比较

治疗后,两组 PEF、FEV1 均较治疗前上升,且研究组以上指标均明显高于对照组,差异有统计学意义($P<0.05$),见表5。

治疗前,两组 PEF、FEV1 比较差异无统计学意义($P>0.05$);

表4 两组治疗前后肺通气功能的比较($\bar{x} \pm s$)

Table 4 Comparison of the pulmonary ventilation between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n	Time	PEF(%)	FEV1(%)
Control group	46	Before treatment	70.50 $\pm$ 9.56	68.12 $\pm$ 7.51
		After treatment	75.50 $\pm$ 9.03 ^a	73.20 $\pm$ 9.41 ^a
Research group	42	Before treatment	72.61 $\pm$ 8.42	66.44 $\pm$ 8.60
		After treatment	81.41 $\pm$ 12.84 ^{a #}	79.53 $\pm$ 10.42 ^{a #}

Note: Compared with the control group, [#] $P<0.05$; Compared with the same group before treatment, ^a $P<0.05$.

2.6 两组不良反应发生情况比较

应发生率比较差异无统计学意义($P>0.05$),见表5。

两组均有胃肠道反应、皮疹和声嘶发生2,组间总不良反

表5 两组不良反应发生情况比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions between the two groups [case (%)]

Groups	n	Gastrointestinal reaction	Rash	Sonar	Total adverse reaction rate
Control group	46	2(4.34)	2(4.34)	1(2.17)	5(10.87)
Research group	42	2(4.76)	3(7.14)	1(2.38)	6(14.29)

3 讨论

支气管哮喘是临床最常见的呼吸道超敏反应之一,可引起多种症状,流行病学研究显示^[10],小儿过敏性哮喘的发生率呈上升趋势,已成为危害儿童健康的常见症候群。遗传学研究认为^[11]小儿支气管哮喘具有一定的家族聚集倾向,是复杂的多基因、

多因素遗传病。Diao M 等^[12]报道基因位点多态性和哮喘易感性有良好关系,并表明携带 MS4A2Glu237Gly 突变者乙酰甲胆碱支气管试验、草放射过敏原吸附试验及屋尘螨皮试试验的测试阳性率明显上升。有研究表明^[13]ADRB2 和 ALOX5 为儿童哮喘的重要候选基因。临床用药可按照患者的特殊个体化基因选择药物和剂量,从而提高临床用药的有效性及安全性,减少药

物治疗的风险。

目前,小儿支气管哮喘主要通过药物控制,其中吸入性糖皮质激素的疗效得到广泛认可,能够起到免疫抑制、抑制补体参与炎症反应、降低毛细血管通透性等作用,且可利于气道平滑肌 β 2受体功能的重建,加强气道对 β 2受体激动剂的敏感性,从而减轻气道的过敏反应^[14]。吸入用布地奈德具有亲和力高、副作用小等特点,能够诱导脂皮素的合成从而抑制前列腺素、白三烯、血小板活化因子等脂类炎症介质的生成及释放^[15]。另外,布地奈德可促进血管紧张素II表达,减轻多种活性物质的致炎、扩张血管等反应。布地奈德经雾化吸入可提高局部呼吸道的药物浓度,更易作用于全肺组织,确保疗效的发挥,更有利于患儿的配合,其经口咽部吸入可提高用药安全性^[16]。但有研究报道^[17]布地奈德对白三烯的抑制作用较弱,因此对部分哮喘患儿的疗效欠佳。且有研究认为^[18]布地奈德可能对患儿身高产生一定程度的抑制作用。本研究结果显示吸入布地奈德治疗后有少数患儿疗效评价为无效,表明其效果有待提高。

白三烯作为一种促炎介质可增加血管通透性,促进嗜酸性粒细胞的浸润,引起气道高反应性,导致支气管平滑肌痉挛^[19]。白三烯受体拮抗剂可选择性地抑制白三烯多肽活性,阻断白三烯和受体结合,减轻支气管痉挛。孟鲁斯特纳为其代表药物,能够竞争性的阻断过敏介质作用,阻断器官对白三烯的反应,减轻呼吸道炎症,为安全、高效的抗过敏药物^[20]。研究显示^[21] ALOX5 为白三烯合成的关键酶,白三烯调节剂可通过抑制 ALOX5 干预白三烯阻断或合成半胱氨酰白三烯受体药物,提高疗效。一项随机对照研究报道^[22]孟鲁斯特纳对毛屑、花粉等变异原和冷空气刺激、二氧化硫等所致的炎症反应均有抑制作用。有研究显示^[23]糖皮质激素吸入联合白三烯受体拮抗剂在小儿哮喘治疗上有一定优势。本研究结果显示 41 例哮喘患儿经布地奈德联合孟鲁斯特纳治疗后仅 1 例患儿无效,气促、哮喘音、肺部啰音、咳嗽消失时间也相对较少,表明二者联合的疗效较高。

研究表明^[24],多种细胞因子均参与了支气管哮喘的慢性气道炎症反应,其中 EOS 在气道黏膜内聚集、激活可起到直接作用。激活的 EOS 能够分泌血小板活化因子、白三烯、ECP 等炎症介质,引起组织损伤,促进支气管平滑肌的收缩,导致黏膜水肿,产生气道高反应及哮喘发作。ECP 是 EOS 活化后生成的毒性蛋白,其浓度和激活的 EOS 数目有良好的相关性,为 EOS 激活标志,是反映哮喘气道炎症的敏感指标^[25]。IgE 在机体免疫反应中有重要作用,可介导 EOS 释放大量的碱性蛋白,并作用于气道上皮细胞,导致气道炎症反应^[26]。IL-4 可促进 T 细胞及 B 细胞增殖,且可诱导 B 细胞分化为 IgE,刺激肥大细胞分泌并合成炎症介质,导致高反应性,引起疾病发作。Tsai MK 等^[27]研究报道哮喘患儿外周血中 ECP、EOS 等浓度明显上升,并指出其水平和疾病程度、药物疗效有一定相关性。本研究结果治疗后患儿 ECP、EOS、IgE 及 IL-4 水平均下降,且布地奈德联合孟鲁斯特纳组下降更明显,说明二者联合应用能够减轻气道的高反应,考虑与孟鲁斯特纳能够调节机体 Th1/Th2 反应,从而抑制 IL-4 生成,EOS 的增殖、分化,减轻机体炎症反应^[28,29]。进一步分析发现布地奈德联合孟鲁斯特纳治疗后 PEF、FEV1 较高,证实二者联合的疗效。两组用药期间均有少数患儿发生胃肠道反应、皮疹和声嘶发生等不适反应,但症状较为轻微,未产

生严重后果,安全性高。

综上所述,长期吸入布地奈德联合孟鲁斯特纳可提高过敏性哮喘基因阳性患儿的疗效,更能减轻患儿症状,控制气道炎症反应,提高肺功能。但本研究由于随访时间较短,且未观察远期疗效,结果可能有一定局限性,有待进一步研究以明确。

参考文献(References)

- [1] Lazarus SC, Krishnan JA, King TS, et al. Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level[J]. N Engl J Med, 2019, 380(21): 2009-2019
- [2] Alherbish M, Mobaireek KF, Alangari AA. Admission predictability of children with acute asthma[J]. Ann Thorac Med, 2018, 13(1): 36-41
- [3] Nasser MZ, Ezzat DA. Association of -308G/A Polymorphism and Serum Level of TNF- α with Bronchial asthma in Children[J]. Egypt J Immunol, 2018, 25(2): 117-124
- [4] Wang AL, Qiu W, DeMeo DL, et al. DNA methylation is associated with improvement in lung function on inhaled corticosteroids in pediatric asthmatics[J]. Pharmacogenet Genomics, 2019, 29(3): 65-68
- [5] Gaufrin T, Tobin NH, Aldrovandi GM. The importance of the microbiome in pediatrics and pediatric infectious diseases[J]. Curr Opin Pediatr, 2018, 30(1): 117-124
- [6] Singh A, Nandan D, Dewan V, et al. Comparison of clinical effects of beclomethasone dipropionate & budesonide in treatment of children with mild persistent asthma: A double-blind, randomized, controlled study[J]. Indian J Med Res, 2016, 144(2): 250-257
- [7] Razi CH, Cörit N, Andran N. Budesonide reduces hospital admission rates in preschool children with acute wheezing[J]. Pediatr Pulmonol, 2017, 52(6): 720-728
- [8] Kim CK, Callaway Z, Park JS, et al. Montelukast Reduces Serum Levels of Eosinophil-Derived Neurotoxin in Preschool Asthma[J]. Allergy Asthma Immunol Res, 2018, 10(6): 686-697
- [9] Jean T, Yang SJ, Crawford WW, et al. Development of a pediatric asthma predictive index for hospitalization [J]. Ann Allergy Asthma Immunol, 2019, 122(3): 283-288
- [10] Rafeeq MM, Murad H. Evaluation of drug utilization pattern for patients of bronchial asthma in a government hospital of Saudi Arabia [J]. Niger J Clin Pract, 2017, 20(9): 1098-1105
- [11] Törmänen S, Terasjärvi J, Lauhkonen E, et al. TLR5 rs5744174 gene polymorphism is associated with the virus etiology of infant bronchiolitis but not with post-bronchiolitis asthma[J]. Health Sci Rep, 2018, 1(6): e38
- [12] Diao M, Min J, Guo F, et al. Effects of salbutamol aerosol combined with magnesium sulfate on T-lymphocyte subgroup and Th1/Th2 cytokines of pediatric asthma[J]. Exp Ther Med, 2017, 13(1): 117-120
- [13] Peters MC, Ringel L, Dyjack N, et al. A Transcriptomic Method to Determine Airway Immune Dysfunction in T2-High and T2-Low Asthma[J]. Am J Respir Crit Care Med, 2019, 199(4): 465-477
- [14] Podlecka D, Malewska-Kaczmarek K, Jerzyńska J, et al. Secondhand smoke exposure increased the need for inhaled corticosteroids in children with asthma [J]. Ann Allergy Asthma Immunol, 2018, 121(1): 119-121
- [15] Saito M, Kikuchi Y, Kawarai Lefor A, et al. High-dose nebulized budesonide is effective for mild asthma exacerbations in children under 3 years of age [J]. Eur Ann Allergy Clin Immunol, 2017, 49(1):

- 22-27
- [16] Fielding S, Pijnenburg M, de Jongste JC, et al. Change in FEV1 and Feno Measurements as Predictors of Future Asthma Outcomes in Children[J]. Chest, 2019, 155(2): 331-341
- [17] Saito M, Kikuchi Y, Kawai A, et al. High-dose nebulized budesonide is effective for mild asthma exacerbations in children under 3 years of age [J]. Eur Ann Allergy Clin Immunol, 2017, 49(1): 22-27
- [18] Maas BM, Wang J, Cooner F, et al. Bone Mineral Density to Assess Pediatric Bone Health in Drug Development [J]. Ther Innov Regul Sci, 2017, 51(6): 756-760
- [19] Keskin O, Arik Yilmaz E, Motzkus C, et al. The effect of montelukast on early-life wheezing: A randomized, double-blinded placebo-controlled study[J]. Pediatr Allergy Immunol, 2018, 29(1): 50-57
- [20] Kim CK, Callaway Z, Park JS, et al. Montelukast Reduces Serum Levels of Eosinophil-Derived Neurotoxin in Preschool Asthma[J]. Allergy Asthma Immunol Res, 2018, 10(6): 686-697
- [21] Magpuri AT, Dixon JK, McCorkle R, et al. Adapting an Evidence-Based Pediatric Acute Asthma Exacerbation Severity Assessment Tool for Pediatric Primary Care[J]. J Pediatr Health Care, 2018, 32(1): 10-20
- [22] Castro-Rodriguez JA, Rodriguez-Martinez CE, et al. Daily inhaled corticosteroids or montelukast for preschoolers with asthma or recurrent wheezing: A systematic review [J]. Pediatr Pulmonol, 2018, 53(12): 1670-1677
- [23] Trinh HKT, Nguyen TVT, Choi Y, et al. The synergistic effects of clopidogrel with montelukast may be beneficial for asthma treatment [J]. J Cell Mol Med, 2019, 23(5): 3441-3450
- [24] Rafeeq MM, Murad H. Evaluation of drug utilization pattern for patients of bronchial asthma in a government hospital of Saudi Arabia [J]. Niger J Clin Pract, 2017, 20(9): 1098-1105
- [25] Ross MK, Yoon J, van der Schaar A, et al. Discovering Pediatric Asthma Phenotypes on the Basis of Response to Controller Medication Using Machine Learning [J]. Ann Am Thorac Soc, 2018, 15(1): 49-58
- [26] Kansal P, Nandan D, Agarwal S, et al. Correlation of induced sputum eosinophil levels with clinical parameters in mild and moderate persistent asthma in children aged 7-18 years [J]. J Asthma, 2018, 55(4): 385-390
- [27] Tsai MK, Lin YC, Huang MY, et al. The effects of asthma medications on reactive oxygen species production in human monocytes[J]. J Asthma, 2018, 55(4): 345-353
- [28] Fable JM, Fernandez M, Goodine S, et al. Retrospective Comparison of Fluticasone Propionate and Oral Viscous Budesonide in Children With Eosinophilic Esophagitis[J]. J Pediatr Gastroenterol Nutr, 2018, 66(1): 26-32
- [29] Chikani UN, Ibekwe MU, Oguonu T, et al. Steroid-induced impairment of glucose tolerance: Prevalence among pediatric patients on long-term steroid use in Nigeria [J]. Pediatr Diabetes, 2017, 18(8): 942-946
-
- (上接第 2678 页)
- [27] Amin A, Peters R, Verstraaten M, et al. Baseline NT-ProBNP level predicts success of cardioversion of atrial fibrillation with flecainide [J]. Neth Heart J, 2015, 23(3): 182-189
- [28] Deftereos S, Giannopoulos G, Kossyvakis C, et al. Short-term fluctuations of plasma NT-proBNP levels in patients with new-onset atrial fibrillation: a way to assess time of onset? [J]. Heart, 2010, 96(13): 1033-1036
- [29] Kallergis EM, Manios EG, Kanoupakis EM, et al. Effect of sinus rhythm restoration after electrical cardioversion on apelin and brain natriuretic peptide prohormone levels in patients with persistent atrial fibrillation[J]. Am J Cardiol, 2010, 105(1): 90-94
- [30] Möllmann H, Weber M, Elsässer A, et al. NT-ProBNP predicts rhythm stability after cardioversion of lone atrial fibrillation[J]. Circ J, 2008, 72(6): 921-925
- [31] Stoneman P, Gilligan P, Mahon P, et al. Chemical cardioversion of recent-onset atrial fibrillation in the emergency department using vernakalant hydrochloride achieves safe and rapid restoration of sinus rhythm and facilitates same day discharge[J]. Irish Journal of Medical Science, 2017, 186(4): 903-908
- [32] Farkowski MM, Maciag A, Zurawska M, et al. Clinical effectiveness and safety of antazoline-based therapy in patients with stable coronary artery disease undergoing pharmacological cardioversion of short-duration atrial fibrillation in the emergency department[J]. Cardiovascular therapeutics, 2018, 36(6): e12469