·临床研究·

西格列汀联合二甲双胍治疗老年2型糖尿病疗效分析

黄金华
(中关村医院内分泌科,北京 100190)

【摘 要】 **目的** 探讨单服二甲双胍(metformin)治疗未达标的老年2型糖尿病患者(T2DM)加用西格列汀(sitagliptin)的有效性及安全性。**方法** 入选2015年5月至2016年9月中关村医院内分泌科单服二甲双胍控制不佳的老年T2DM患者52例,其中男性30例,女性22例,年龄65~78(68.0±8.0)岁。随机分成西格列汀组和阿卡波糖(acarbose)组,每组26例(男性15例,女性11例)。西格列汀组患者口服西格列汀100 mg/次,1次/d,阿卡波糖组患者口服阿卡波糖50 mg/次,3次/d,两组患者同时口服二甲双胍500 mg/次,3次/d,连续治疗12周。观察两组患者服药12周后空腹血糖(FPG)、餐后2 h血糖(2hPG)、糖化血红蛋白(HbA1c)等指标变化,并记录低血糖、胃肠道不良反应的发生情况。**结果** 两组患者治疗前FPG、2hPG和HbA1c差异均无统计学意义($P>0.05$);治疗12周后,两组患者FPG、2hPG和HbA1c较治疗前均明显降低,并且西格列汀组较阿卡波糖组2hPG和HbA1c下降更显著,差异有统计学意义($P<0.05$)。治疗期间两组患者无低血糖发生,阿卡波糖组4例发生腹胀,排气增加,两组患者不良反应发生差异无统计学意义($P>0.05$)。**结论** 西格列汀与二甲双胍联用治疗T2DM患者疗效显著且安全。

【关键词】 西格列汀;阿卡波糖;二甲双胍;2型糖尿病;老年人
【中图分类号】 R587.1 【文献标志码】 A 【DOI】 10.11915/j.issn.1671-5403.2017.05.083

Efficacy of sitagliptin combined with metformin in treatment of type 2 diabetes mellitus in the elderly

HUANG Jin-Hua
(Department of Endocrinology, Zhongguancun Hospital, Beijing 100190, China)

【**Abstract**】 **Objective** To compare the efficacy and safety of combining sitagliptinin to therapy type 2 diabetes mellitus (T2DM) of elderly patients with inadequate glycemic controlled by metformin monotherapy. **Methods** A total of 52 T2DM elderly patients [30 males and 22 females, at an age of (68.0±8.0) years, ranging from 65 to 78] with inadequate glycemic controled by metformin monotherapy admitted in our department from May 2015 to September 2016 were recruited in this study. They were randomly divided into sitagliptin group and acarbose group, with 26 ones in each. Besides oral administration of 500 mg metformin (3 times per day), the former group was treated with 100 mg sitagliptin (once per day), and the latter with 50 mg acarbose (3 times per day), for 12 consecutive weeks. Then fasting plasma glucose (FBG), 2-hour postprandial glucose (2hPG), hemoglobin A1c (HbA1c) and body mass index (BMI) were measured in the 2 groups. The incidences of hypoglycemia and gastrointestinal adverse reactions were observed. **Results** No difference was seen in the FBG, 2hPG and HbA1c in the 2 groups before treatment ($P>0.05$). After the treatment, the above 3 indicators were significantly reduced ($P<0.05$). The declines of 2hPG and HbA1c were more obvious in the sitagliptin group than acarbose group ($P<0.05$). No hypoglycemia was observed during treatment. In acarbose group, 4 cases complained of abdominal distention and increased flatus passage. No statistical difference was observed in gastrointestinal adverse reactions between two groups ($P>0.05$). **Conclusion** Combined of sitagliptin with metformin shows significant efficacy and safety in treatment of T2DM elderly patients.

【**Key words**】 sitagliptin; acarbose; metformin; type 2 diabetes mellitus; aged

Corresponding author: *HUANG Jin-Hua*, *E-mail*: *huangjinhua@yeah.net*

目前我国有糖尿病患者约9000万,城镇发病率约9.7%[1]。高胰岛素血症和胰岛素抵抗是2型糖尿病(type 2 diabetes mellitus,T2DM)发病机制的中心环节,高胰岛素血症降低胰岛素与受体的亲和力,

收稿日期:2016-12-03;**修回日期**:2016-12-21
通信作者:黄金华,E-mail:huangjinhua@yeah.net

导致胰岛素的作用受阻,引发胰岛素抵抗,从而需B细胞分泌和释放更多的胰岛素,加重高胰岛素血症、糖代谢紊乱和B细胞功能不足的恶性循环最终导致B细胞功能严重缺陷,引发T2DM[2]。因此,早期发现和诊断糖尿病,积极给予有效而合理的治疗,对控制病情和保护胰岛B细胞的功能非常重要。二甲双胍常作为治疗T2DM的首选药物,本研究探讨了二甲双胍联用二肽基肽酶-4(dipeptidyl peptidase Ⅳ,DPP-4)抑制剂(西格列汀或阿卡波糖)对老年T2DM的有效性及安全性。

1 对象与方法

1.1 研究对象

入选2015年5月至2016年9月中关村医院内分泌科单服二甲双胍控制不佳的老年T2DM患者52例,其中男性30例,女性22例,年龄65~78(68.0±8.0)岁,随机分成西格列汀组和阿卡波糖组,每组26例(男性15例,女性11例)。纳入标准:符合世界卫生组织(World Health Organization,WHO)T2DM诊断标准;无严重心脑血管疾病、糖尿病急性合并性疾病(如糖尿病酮症酸中毒等)及其他内分泌代谢疾病。本研究已通过医院伦理委员会批准,所有研究对象均签署知情同意书。

1.2 方法

所有患者严格控制饮食,西格列汀组患者给予西格列汀(sitagliptin,美国默沙东制药有限公司)100 mg/次,1次/d,口服;阿卡波糖组患者给予阿卡波糖(acarbose,德国拜耳医药有限公司)50 mg/次,3次/d,口服,餐时嚼服。两组患者均同时口服二甲双胍(metformin,中美上海施贵宝制药有限公司)500 mg/次,3次/d。连续治疗12周。血糖控制目标为空腹血糖(fasting plasma glucose,FPG)3.9~7.0 mmol/L,餐后2 h血糖(2 hours postprandial glucose,2hPG)<10.0 mmol/L。

1.3 检测指标

检测两组患者治疗前和治疗12周后糖化血红蛋白(hemoglobin A1c,HbA1c)、FPG、2hPG、体质量指数(body mass index,BMI)、丙氨酸氨基转移酶(alanine amino transferase,ALT)、天冬氨酸氨基转移酶(aspartate amino transferase,AST)、血尿素氮(blood urea nitrogen,BUN)、血肌酐(serum creatinine,SCr)、甘油三酯(triglycerides,TG)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol,LDL-C)、血清淀粉酶(amylase,AMS)水平,并统计胃肠道不良反应、低血糖发生次数及药物不良反应相关事件。

1.4 统计学处理

采用SPSS17.0统计软件对数据进行分析。计量资料用均数±标准差($\bar{x}\pm s$)表示,两组比较采用t检验。计数资料用百分率表示,组间比较用χ^2检验。以$P<0.05$为差异有统计学意义。

2 结 果

2.1 临床资料比较

西格列汀组患者与阿卡波糖组的年龄差异无统计学意义[(68.00±7.60) *vs* (69.00±4.70)岁,$P>0.05$]。治疗前,两组患者在腰围、臀围、BMI和肝肾功能方面差异无统计学意义($P>0.05$),治疗12周后,两组患者与治疗前相比,上述指标均无显著性改善($P>0.05$;表1)。

2.2 两组患者血糖水平比较

两组患者治疗前FPG、2hPG和HbA1c差异均无统计学意义($P>0.05$)。治疗12周后,两组患者FPG、2hPG和HbA1c较治疗前均明显降低,并且治疗后西格列汀组患者较阿卡波糖组患者2hPG和HbA1c下降更显著,差异有统计学意义($P<0.05$;表2)。

2.3 不良反应

治疗期间两组均无低血糖发生,即时血糖水平均>3.9 mmol/L。阿卡波糖组4例发生腹胀、排气增加。两组患者不良反应发生情况之间差异无统计学意义($P>0.05$)。

3 讨 论

肠促胰液素是进餐后由肠道细胞分泌的多肽类激素,参与葡萄糖稳态调控[3],是治疗T2DM患者的新靶点。包括胰高糖素样多肽-1(glucagon like peptide-1,GLP-1)和葡萄糖依赖性促胰岛素分泌多肽(glucose-dependent insulinotropicploypeptide,GIP)[4]。GLP-1的生理功能主要包括促胰岛素分泌、胰岛B细胞增殖并抑制其凋亡、减缓胃排空、抑制餐后胰高血糖素分泌、减少肝糖元合成、提高胰岛素敏感性及控制食欲等[5]。此外,胰岛素样生长因子结合蛋白1(insulin like growth factor binding protein 1,IGFBP-1)水平升高和特异表达与胰岛素抵抗和血糖异常相关,GLP-1可通过抑制IGFBP-1表达从而影响血糖水平[6]。但GLP-1半衰期很短,仅1~2 min,极易被体内的DPP-4降解[7],难以应用于临床。磷酸西格列汀是一种DPP-4抑制剂,可抑制DPP-4活性、提高GLP-1水平[8]、增加葡萄糖摄取、减低肝糖原输出和生成[9],可刺激胰岛素分泌,并降低循环中

表1 两组患者临床资料比较

Table 1 Comparison of clinical data between two groups ($n=26, \bar{x} \pm s$)

Item	Sitagliptin group		Acarbose group	
	Before therapy	After therapy	Before therapy	After therapy
Waist circumference(cm)	85.30±7.00	83.50±4.60	86.90±5.80	86.70±5.00
Hip circumference(cm)	85.10±4.40	84.70±3.90	86.50±2.60	86.50±1.80
BMI(kg/m^2)	25.87±0.57	24.16±0.34	25.79±0.62	24.35±0.48
ALT(U/L)	25.90±7.54	26.10±6.37	21.70±6.51	21.50±50.42
AST(U/L)	63.50±9.32	65.90±6.49	61.60±8.75	60.30±7.56
TC(mmol/L)	4.18±1.39	4.06±1.34	4.09±1.02	4.01±0.57
TG(mmol/L)	1.26±0.51	1.20±0.40	1.30±0.42	1.28±0.52
LDL-C(mmol/L)	2.72±0.45	2.18±0.26	2.76±0.32	2.22±0.73
HDL-C(mmol/L)	0.90±0.31	0.91±0.32	0.87±0.26	0.88±0.20
mALB(mg/L)	10.24±0.02	9.78±0.13	8.53±7.21	8.46±6.19
AMS(U/L)	63.50±9.32	62.90±6.49	61.60±8.75	60.30±7.56
TBIL(μmol)	16.10±3.38	15.90±2.49	15.40±4.30	15.00±3.26
DBIL(μmol/L)	15.40±4.16	13.80±3.73	15.70±4.27	15.30±3.61
BUN(mmol/L)	4.79±2.08	4.81±1.65	5.36±1.49	4.87±1.52
SCr(μmol/L)	65.20±7.64	63.90±5.58	63.90±5.58	63.50±7.26

BMI: bodymass index; ALT: alanine amino transferase; AST: aspartate amino transferase; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; mALB: micro albumin; AMS: amylase; TBIL: total bilirubin; DBIL: conjugated bilirubin; BUN: blood urea nitrogen; SCr: serum creatinine

表2 两组患者血糖水平比较

Table 2 Comparison of glucose level between two groups ($n=26, \bar{x} \pm s$)

Item	Sitagliptin group		Acarbose group	
	Before therapy	After therapy	Before therapy	After therapy
FPG(mmol/L)	9.75±1.24	6.59±1.54*	9.69±1.31	6.88±1.62*
2hPG(mmol/L)	13.92±2.21	8.75±1.45*#	13.85±2.06	8.99±1.36*
HbA1c(%)	9.36±1.28	7.03±0.36*#	9.31±1.34	7.10±1.34*

FPG: fasting plasma glucose; 2hPG: 2 hours postprandial glucose; HbA1c: hemoglobin A1c. Compared with before therapy, *$P<0.05$; compared with acarbose group, #$P<0.05$

胰高糖素水平,有效降低血糖,从而保护胰岛功能[10,11]。相比传统磺脲类药物,该药不增加体质量,且低血糖发生风险更低,表明该药物可能更适用于老年T2DM患者。本研究表明,老年T2DM患者如单用二甲双胍治疗控制血糖不佳,可联合服用西格列汀,相比联合服用阿卡波糖组患者,FPG、2hPG和HbA1c可得到明显改善,且患者肝肾功能无显著变化,AMS水平无明显升高,提示短期使用西格利汀并不导致肝肾功能异常或胰腺炎。

本研究显示,二甲双胍加服西格列汀可安全、有效地降低血糖,改善胰岛B细胞功能,增加血糖达标率[12],且不增加心力衰竭患者风险[13],具有较好的安全性和有效性[14,15]。但西格列汀作为新型降糖药,还需进一步评价。鉴于本研究病例数有限,研究时间短,可扩大样本量及延长观察时间进一步研究。

【参考文献】

[1] Yang W, Lu J, Weng J, *et al*. Prevalence of diabetes among men and women in China[J]. N Engl J Med, 2010, 362(12): 1090-1101. DOI: 10.1056/NEJMoa0908292.

[2] Ma Y, Wang Y, Huang Q, *et al*. Impaired β cell function in Chinese newly diagnosed type 2 diabetes mellitus with hyperlipidemia[J]. J Diabetes Res, 2014, 2014: ID493039. DOI: 10.1155/2014/493039.

[3] Karabulut S, Coskun ZM, Bolkent S. Immunohistochemical, apoptotic and biochemical changes by dipeptidyl peptidase-4 inhibitor-sitagliptin in type-2 diabetic rats[J]. Pharmacol Rep, 2015, 67(5): 846-853. DOI: 10.1016/j.pharep.2015.01.010.

[4] Mu J, Woods J, Zhou YP, *et al*. Chronic inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic beta-cell mass and function in a rodent model of type 2 diabetes[J]. Diabetes, 2006, 55(6): 1695-1704. DOI: 10.2337/db05-1602.

[5] 董立厚. GLP-1与2型糖尿病:生理学和临床研究进展[J].

国外医学药学分册, 2007, 4(34):151.
Dong LH. GLP-1 and type-2 diabetes: physiology and clinical research progress[J]. Foreign Med Sci Sect Pharm, 2007, 4(34): 151.

[6] Arnetz L, Hage C, Ekberg NR, *et al*. Improved glycemic control due to sitagliptin is not related to cortisol or the surrogate marker IGFBP-1 for hepatic insulin sensitivity[J]. Growth Horm IGF Res, 2015, 25(6): 298-303. DOI: 10.1016/j.ghir.2015.07.009.

[7] 庾 辉. 胰高血糖素样肽-1及类似物在心血管疾病的作用及研究进展[J]. 心血管病学进展, 2011, 9(32): 727-728.
Yu H. Research progress of glucagon-like peptide-1 and analogues for cardiovascular disease [J]. Adv Cardiovasc Dis, 2011, 9(32): 727-728.

[8] Kim JH. Effects of sitagliptin on insulin and glucagon levels in type 2 diabetes mellitus[J]. Diabetes Metab J, 2015, 39(4): 304-306. DOI: 10.4093/dmj.2015.39.4.304.

[9] 廖二元. 内分泌代谢病学[M]. 北京: 人民卫生出版社, 2012: 1261-1262.
Liao EY. Endocrine Metabolism Epidemiology [M]. Beijing: People's Medical Publishing House, 2012: 1261-1262.

[10] Guthrie RM. Evolving therapeutic options for type 2 diabetes mellitus: an overview[J]. Postgrad Med, 2012, 124(6): 82-89. DOI: 10.3810/pgm.2012.11.2614.

[11] Lee M, Rhee MK. Sitagliptin for type 2 diabetes: a 2015 update[J]. Expert Rev Cardiovasc Ther, 2015, 13(6): 597-610. DOI: 10.1586/14779072.2015.1046840.

[12] Oguma T, Nakayama K, Kuriyama C. Intestinal sodium glucose cotransporter 1 inhibition enhances glucagon-like peptide-1 secretion in normal and diabetic rodents[J]. J Pharmacol Exp Ther, 2015, 354(3): 279-289. DOI: 10.1124/jpet.115.225508.

[13] Ryan G. Dipeptidyl peptidase-4 inhibitor use in patients with type 2 diabetes and cardiovascular disease or risk factors[J]. Postgrad Med, 2015, 127(8): 842-54. DOI: 10.1080/00325481.2015.1095616.

[14] Monami M, Iacomelli I, Marchionni N, *et al*. Dipeptydil peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials[J]. Nutr Metab Cardiovasc Dis, 2010, 20(4): 224-235. DOI: 10.1016/j.numecd.2009.03.015.

[15] Shankar RR, Xu L, Golm GT, *et al*. A comparison of glycaemic effects of sitagliptin and sulfonylureas in elderly patients with type 2 diabetes mellitus [J]. Int J Clin Pract, 2015, 69(6): 626-631. DOI: 10.1111/ijcp.12607.

（编辑：王彩霞）

·消 息·

《中华老年多器官疾病杂志》调整文末参考文献著录格式

自2017年1月起，我刊调整录用稿件的文末参考文献著录格式：(1)中文参考文献采用中英文双语著录，中文在前，英文在后；(2)参考文献如有“数字对象唯一标识符(DOI)”编码，应著录，列于末尾。

示例：

[1] Williamson JD, Supiano MA, Applegate WB, *et al*. Intensive *vs* standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial[J]. JAMA, 2016, 315(24): 2673-2682. DOI: 10.1001/jama.2016.7050.

[2] 李 葳, 邓雅丽, 卓 琳, 等. 阿司匹林对于心血管疾病一级预防的效果及安全性的系统综述及meta分析[J]. 中华老年多器官疾病杂志, 2016, 15(12): 896-901. DOI: 10.11915/j.issn.1671-5403.2016.12.215.
Li W, Deng YL, Zhuo L, *et al*. Effect and safety of aspirin for primary prevention of cardiovascular diseases: a systematic review and meta analysis[J]. Chin J Mult Organ Dis Elderly, 2016, 15(12): 896-901. DOI: 10.11915/j.issn.1671-5403.2016.12.215.

地址：100853 北京市复兴路28号，《中华老年多器官疾病杂志》编辑部
电话：010-66936756
网址：www.mode301.cn
E-mail：zhlndqg@mode301.cn