UDC [[616.5-036.17-085.357:577.175.53]-008.9:547.455.623]-084-08

PROPHYLAXIS AND THERAPY OF IMPAIRED GLUCOSE TOLERANCE IN LONG-TERM THERAPY OF THE PATIENTS WITH SEVERE DERMATOSES WITH GLUCOCORTICOSTEROID HORMONES

Y. F. Kutasevych[1], O. O. Levchenko[1, 2], M. M. Popov[2]
[1]SE «Institute of dermatology and venerology of the NAMSU», Kharkiv, Ukraine
[2]V. N. Karazin Kharkiv National University, Kharkiv, Ukraine

Impaired glucose tolerance (IGT) is the most wide-spread complication of long-term therapy of severe dermatoses with glucocorticoid hormones among possible steroid-induced disturbances of carbohydrate metabolism being also a component part of the conception « state prior to the development of diabetes». The mentioned complication leads to the development of cardiovascular pathology which in its turn worsens both the general state of the patient and aggravates the dermatosis course. In this connection the work on prophylaxis and therapy of steroid-induced IGT with metformin preparation having a number of therapeutic effects on human organism besides main hypoglycemic activity in patients with skin diseases was carried out.

KEY WORDS: severe dermatoses, protracted, glucocorticosteroid hormones, impaired glucose tolerance, cardio-vascular system, prophylaxis, therapy, metformin

ПРОФІЛАКТИКА ТА ЛІКУВАННЯ ПОРУШЕНОЇ ТОЛЕРАНТНОСТІ ДО ГЛЮКОЗИ У ХВОРИХ НА ТЯЖКІ ДЕРМАТОЗИ ПРИ ДОВГОТРИВАЛІЙ ТЕРАПІЇ ГЛЮКОКОРТИКОСТЕРОЇДНИМИ ГОРМОНАМИ

Я. Ф Кутасевич[1], О. О. Левченко[1, 2], М. М. Попов[2]
[1]ДУ «Інститут дерматології та венерології НАМНУ», Харків, Україна
[2]Харківський національний університет імені В. Н. Каразіна, Україна

Порушена толерантність до глюкози (ПТГ) є найбільш поширеним ускладненням довготривалої терапії глюкокотикостероїдними гормонами тяжких дерматозів серед можливих стероїд-індукованих порушень вуглеводного обміну і також є складовою частиною поняття «переддіабет». Це ускладнення призводить до розвитку патології серцево-судинної системи, що, в свою чергу, погіршує як загальний стан пацієнта так і перебіг дерматоза. У зв'язку з цим була проведена робота по профілактиці та лікуванню стероїд-індукованої ПТГ у хворих на тяжкі шкірні захворювання препаратом метформін, який крім основної цукрознижуючої дії має ще ряд лікувальних ефектів на організм людини.

КЛЮЧОВІ СЛОВА: тяжкі дерматози, довготривала терапія, глюкокортикостероїдні гормони, порушена толерантність до глюкози, серцево-судинна система, профілактика, лікування, метформін

ПРОФИЛАКТИКА И ЛЕЧЕНИЕ НАРУШЕННОЙ ТОЛЕРАНТНОСТИ К ГЛЮКОЗЕ У БОЛЬНЫХ ТЯЖЕЛЫМИ ДЕРМАТОЗАМИ ПРИ ДЛИТЕЛЬНОЙ ТЕРАПИИ ТЯЖЕЛЫХ ДЕРМАТОЗОВ ГЛЮКОКОРТИКОСТЕРОИДНЫМИ ГОРМОНАМИ

Я. Ф. Кутасевич[1], О. А. Левченко[1, 2], Н. Н. Попов[2]
[1]ГУ «Институт дерматологии и венерологии НАМНУ», Харьков, Украина
[2]Харьковский национальный университет имени В. Н. Каразина, Украина

Нарушенная толерантность к глюкозе (НТГ) является наиболее распространенным осложнением длительной терапии глюкокортикостероидными гормонами тяжелых дерматозов среди возможных стероид-индуцированных нарушений углеводного обмена и также является составной частью понятия «преддиабет». Данное осложнение приводит к развитию патологии сердечно-сосудистой системы, что, в свою очередь, ухудшает как общее состояние пациента, так и усугубляет течение дерматоза. В связи с этим была проведена работа по профилактике и лечению стероид-индуцированной НТГ у больных тяжелыми кожными заболеваниями препаратом метформин, который помимо основного сахароснижающего действия обладает еще рядом лечебных эффектов на организм человека.

КЛЮЧЕВЫЕ СЛОВА: тяжелые дерматозы, длительная терапия, глюкокортикостероидные гормоны, нарушенная толерантность к глюкозе, сердечно-сосудистая система, профилактика, лечение, метформин

INTRODUCTION

The main aim of patients with severe wide-spread dermatoses treatment is the improvement of the quality of life of the patients at the expense of exacerbation prevention, normal skin function ensuring, normal level of physical activity maintenance, side effect of medications used in therapy expulsion. On the assumption of the leading role of autoimmune processes and inflammation in severe dermatoses pathogenesis therapy foresees the use of immune modulating and anti-inflammatory medications the most effective of which are the glucocorticosteroid hormones (GCs) [1-3], though the long-term taking of the medication from the mentioned group not only provides the curative effect but also disturbs the state of carbohydrate metabolism, particularly causes the development of impaired glucose tolerance (IGT) [3-6]. In the basis of GCs induced IGT the insulin resistance underlies, which is compensated by excess insulin production for a long time and as a result of that the level of glucose in blood remains normal. Though afterwards under insulin resistance growth, the secretory function of ß-cells weakens [6-7]. The clinical manifestation of early phase of insulin secretion disturbance is the development of postprandial hyperglycemia, i.e. impaired glucose tolerance. IGT is the component part of conception «state prior to the development of diabetes», connecting IGT and impaired fasting glucose (IFG). It was stated that the risk of cardio-vascular complications growth is observed already at the stage prior to the development of diabetes and postprandial hyperglycemia (blood plasma glucose level after eating), is an independent risk factor of cardio-vascular complications development and premature death [7-8]. Funagata Diabetes Study also showed that heightened risk of cardio-vascular complications is connected not with IFG, but with IGT development.

Consequently in connection with the mentioned above the treatment must be conducted on the stage of IGT and IFG, preventing the development of the 2nd type diabetes mellitus [9]. It became the ground for the therapeutic and prophylactic method working out of the GCs induced IGT of the patients with severe dermatoses on long-term therapy by GCs on the basis of dermatology department of SE «Institute of dermatology and venereology of the NAMS of Ukraine».

OBJECTIVE

The purpose of the study is to work out prophylaxis and treatment method of impaired glucose tolerance in patients with severe dermatoses on long-term therapy with gluco-corticosteroids.

MATERIALS AND METHODS

72 patients with severe dermatoses were examined: 39 women, 33 men at the age from 35 to 72 years old, among which 21 patients with severe forms of psoriasis, 20 – with true pemphigus, 10 – with erythema multiforme, 1 – with cicatricial pemphigoid, 8 – with chronic eczema, 9 – with vasculitis, 3 – with dermatitis herpetiformis who took GCs from 0,5 to 5 years and more in a dose 5-60 mg per day according to prednisolone (tab. 1).

Table 1

Distribution of the patients according to the forms of dermatoses and duration of systemic glucocrticosteroids taking

Duration of GCs taking	Severe forms of psoriasis	True pemphigus	Erythema multiforme	Vasculitis	Chronic eczema	Dermatitis herpetiformis	Cicatricial pemphigoid
less than 0,5 years	13	7	6	5	6	2	-
up to 1 year	3	8	3	3	2	1	-
up to 5 years	3	3	1	1	-	-	-
more than 5 years	2	2	-	-	-	-	1

For detection of IGT the oral glucosetolerant test (OGTT) was conducted in all patients. Only the patients with the normal indexes of glucose content in serum according to the biochemical blood examination took part in the trial. The participants of the examination took food ration with not more than 250 grams of carbohydtates per day for three days (but not less than 1,75/kg). Blood sampling from the finger on an empty stomach (minimally 12 hours of starvation) was done (the patients excluded the use of alcohol and intense physical loading for 24 hours before the examination). After that they were given the solution (75 g of glucose dissolved in 250 ml of warm water), which they drank during 3-5 minutes. The second blood sampling was done 120 minutes after glucose solution taking (during this period the patient was calmly sitting, not eating, drinking and smoking).

Results of OGTT interpretation:

- Normal tolerance to glucose is characterized by the glycemia level of less than 8 millimoles per liter (< 140 mg/dl) 2 hours after glucose taking;
- Increase of glucose concentration in blood plasma 2 hours after glucose solution taking more than for 7,8 millimoles per liter (> 140 mg/dl), but less than 11,1 millimoles per liter (< 200mg/dl), testifies for impaired glucose tolerance [10-11].

On the basis of the trial with the aim of IGT revealing patients were subdivided into 2 groups. In the first group there were 31 persons in which IGT was revealed on the long-term GCs therapy. In the second group there were 41 patients who showed no disturbances from the side of carbohydrate metabolism before GCs prescription. With the aim of IGT treatment (I group patients) metformin was prescribed in a dose from 500 to 2000 mg per day depending on susceptibility and effectiveness of the preparation during GCs taking. With the aim of IGT development prophylaxis (II group patients) the preparation was prescribed in a dose 500 mg per day simultaneously with the beginning of GCs taking. The control of medication effectiveness was carried out in both groups one month after its prescription. In diseases demanding lifelong GCs taking, metformin was prescribed in interrupted courses of 1-2 months 3-4 times a year. All the patients receiving GCs during the whole course of the main disease therapy kept diet № 9 according to Pevsner.

Metformin is a peroral hypoglycemic medication from the group of biguanides being the first-line remedy in diabetes mellitus of the 2^{nd} type therapy. Sensitivity of periphery tissues to insulin increases under the effect of metformin. The preparation decreases the glucose production by liver on account of liver sensitivity increase to insulin, decrease of gluconeogenesis and glycogenolysis, what leads to decrease of fasting glucose level. Besides angioprotector activity of the medication is its additional privilege because of which it is very useful in case of coronary artery disease [9, 12-13].

Statistical analysis was conducted on each subject by the «Microsoft Excel 2003» program. The arithmetic mean value (M), standard deviation (sd), the error in determining the arithmetic mean indexes (m) were calculated, the authenticity of differences (p) of comparative group averages were determined using the Student-Fisher t-criterion [14].

RESULTS AND DISCUSSION

In estimation of glucose level in blood serum before the beginning of therapy (prescription of systemic GCs) in the I group 120 minutes after glucose solution taking (75 g) the reliable increase of its level in blood was stated: 7,9 ± 0,1 millimoles per liter. In the II group no impaired glucose tolerance was found at examination: 4,7 ± 0,5 millimoles per liter. After metformin prescription while OGTT conducting it was found that in the I group of patients the blood glucose level normalized: 4,4 ± 0,41 millimoles per liter, in the II group of patients this index remained in the normal range: 4,8 ± 0,4 millimoles per liter (tab. 2).

The results of OGTT showed that the use of metformin in complex therapy of patients with severe dermatoses in long-term GCs taking leads to normalization of glucose level in blood and prevents the formation of disturbances of its level in serum.

CONCLUSIONS

1. Metformin is an effective medication that prevents and treats the impaired glucose tolerance in patients with severe dermatoses on long-term therapy with glucocorticosteroid hormons.
2. The used method of examination (oral glucosetolerant test) is accessible in cost and its conducting and can be widely used for

disturbance of carbohydrate metabolism diagnostics and its therapy control in everyday practice of dermatologists.

3. Prescription of metformin during long-term therapy with glucocorticosteroids makes the use of them less dangerous for the patients, preventing the development of of long-term treatment with these drugs, what in its turn improves the quality of dermatoses therapy and sometimes allows to preserve the patients' life (for example, in true pemphigus).

Table 2

Dynamics of the blood glucose level in patients with severe dermatoses during long-term therapy with glucocorticosteroids, (M ± sd)

Glucose of capillary blood, (millimoles per liter)	I group, n=31		II group, n=41		Group of control, n=30	
	On an empty stomach	120 minutes after glucose solution taking (75g)	On an empty stomach	120 minutes after glucose solution taking (75g)	On an empty stomach	120 minutes after glucose solution taking (75g)
before metformin prescription	4,4 ± 0,6	7,9 ± 0,1†	4,8 ± 0,3†	4,7 ± 0,5	4,0 ± 0,33†	4,9 ± 0,41
after metformin prescription	4,3 ± 0,6	4,4 ± 0,4*	5,0 ± 0,1*	4,8 ± 0,4	5,0 ± 0,28*	4,2 ± 0,5

Note: * – differences are reliable ($p < 0,05$) in comparison with the index before metformin prescription;
† - differences are reliable ($p < 0,05$) in comparison with the index after metformin prescription.

PROSPECTS FOR FUTURE STUDIES

The further deeper study of glucocorticosteroids influence on the human organism and possibilities of their side effects prevention will allow to use wider these very strong and still essential medications more effectively not only in the practice of dermatologist but in another glucocorticoids-depending diseases.

REFERENCES

1. Atlas po dermatologii / Martin Reken, Martin Shaler, Elke Zattler, Valter Burgdorf; per. s nem. - M.: MEDpress-inform, 2012.- 408 s.
2. Bortkevich O.P. Suchasni uyavlennya pro spektr zastosuvannya ta bezpeku terapii glukokortikoidami pri revmatichnic khvorobach / O.P. Bortkevich, Y.V. Bilyavska // Ukrainskij revmatologichnij zchurnal. - 2010. - №2(40). - S. 40-50.
3. Lyashyk P.M. Aktualni pitannya sistemnoi terapii glukokortikoidnimi preparatami / P.M. Lyashuk // Mizchnarodnij endokrinologichnij zchurnal. – 2009. – № 2 (20). – S. 99–102.
4. Pankiv V.I. Bolezn Izenko-Kushinga: diagnostika, klinika, lechenie / V.I. Pankiv // Novosti medizini i farmazii. – 2011. – № 16 (379) – S. 27–29.
5. Clore J.N. Glucocorticoid-induced hyperglycemia / J.N. Clore, L. Thurby-Hay // Endocr. Pract. – 2009. – Vol. 15. – P. 469–474.
6. Hoes J.N. Glucose tolerance, insulin sensitivity and β-cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids / J.N.Hoes, M.C. van der Goes, D.H. van Raalte [et al.] // The EULAR Journal. - 2011. - Vol.70, №. 10. – P. 1887-1894.
7. Kim S.Y. Incidence and Risk Factors of Steroid-Induced Diabetes in Patients with Respiratory Disease / S.Y. Kim, C.-G. Yoo, C.T. Lee et al. // Journal of Korean Medical Science. – 2011. – Vol. 26, No. 2. – P. 264–267.
8. Bogun L.V. Sakharnij diabet i soputstvuyushie zabolevaniya vnutrennikh organov / L.V. Bogun, N.A. Yarina // Novosti medizini i farmazii. - 2011. - № 20(392). - S. 20-23.
9. Inzucchi S. Inzucchi Rekomendazii Amerikanskoj diabeticheskoj asoziazii i Evropejskoj assoziazii po izucheniu sakharnogo diabeta. Individualnij podkhod k vedeniu pazientov s giperglikemiej na fone sakharnogo diabeta 2-go typa / S. Inzucchi, R. Bergenstal, J. Buse [et al.] // Novosti medizini i farmazii. - 2012. - № 11(421) - S. 91-107.
10. Rukovodstvo po diagnostike i lecheniu sakharnogo diabeta / Karachenzev Y.I., Mikituk M.R., Polosova L.G., Khizchnyak O.A. - Kh., «S.A.M.», 2007.-244 s.

11. Turnbull F.M. Intensive glucose control and macrovascular outcomes in type 2 diabetes / F.M. Turnbull, C. Abraira // Diabetologia. – 2009 - 52(11): 2288-2298.
12. Kak pravilno lechit sakharnij diabet 2-go typa: prostie prinzipi, spasaushie pazientam zchisn // Ukrainskij medichnij chasopis. - 2012. - № 2(88). - S. 15-18.
13. Mikhalchishin G.P. Metformin novogo pokoleniya: v chem preimushestva? / G.P. Mikhalchishin // Mizchnarodnij endokrinologichnij zchurnal. - 2009. - №2(20). - S.50-52.
14. Lapach S.N. Statisticheskie metodyi v mediko-biologicheskih issledovaniyah s ispolzovaniem EXCEL / S.N. Lapach, A.V. Chubenko, P.N. Babich. – K.: Morion, 2000. – 320 s.