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DYNAMICS OF INSULIN CONSUMPTION IN UKRAINE OVER A PERIOD OF 2008-2012

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Summary: The analysis of insulin agents' consumption in the pharmaceutical market of Ukraine as of the data of years 2008-2012 has been carried out using the ATC/DDD methodology in terms of DDDS/1000 of persons/day. The low level of consumption, compared to the European countries, as well as its reduction, compared to the data of 2008, has been determined. The structural analysis has shown low insulin consumption. The highest consumption level has been determined for the human insulin agent. The data on provision of PD-1 patients with insulin medications, without consideration of PD-2 patients' consumption, evidence the inconsistency of the consumption volume with PD-1 case rate.

Key words: consumption analysis, insulin preparations, pancreatic diabetes

Introduction. The study of insulin medication consumption volume and structure, both in retail and in hospital segment, and the comparison of them with prevalence rate of pancreatic diabetes (PD) in Ukraine enable to evaluate the real provision and consumption structure as of this group of medicaments. The data of this analysis also reflect correspondence of their application to the contemporary treatment strategies and call for revision of PD therapy irrational schemes (less clinically and cost-effective).

Now, a priority issue is application of strategies, providing glycemia stabilization and support of its objective values, which would help to reduce the advanced development of complications, disability, mortality of PD patients and resulting costs for both the state and the patient. Recently, the world insulin market has felt an increase of consumption level of insulin analogous group, having particular advantages over human insulin and insulin of animal origin.

The research has studied volumes and structure of insulin preparations group consumption based on data of hospital and retail segment of pharmaceutical market of Ukraine for evaluation of PD patients provision with insulin preparations.

Materials and methods of study. The target of the study is the insulin group medication consumption data of the market research analytical system "PharmXplorer/Pharmstandard" of "Proxima Research" company. The consumption level of medicinal preparations has been evaluated with ATC/DDD methodology in terms of DDDS/1000 persons/day. This index shows a ratio of the population receiving a certain treatment. A comparative analysis of insulin consumption has been carried out based on data of years 2008-2012.

Results and discussions. The analysis of insulin medication consumption in pharmaceutical market of Ukraine has put its types as follows: group A10A B –ultra-short acting insulin – USAI (analogues of human insulin) and short acting –SAI (soluble engineered human insulin and pig insulin); group A10A C – insulin of action of average duration and its analogues - IADA (engineered human insulin and pig insulin); group A10A E – long acting insulin - LAI (analogues of human insulin); group A10A D - 2-exponential insulin (mixture of SAI and neutral protamine hagedorn and mixture of USAI and neutral protamine hagedorn).

The comparative analysis of insulin preparations consumption within 5 year period has shown the total consumption volume reduction in terms of DDDS/1000 persons/day for 29.65% in 2012 compared to 2008, which is difficult to comment due to the increase of the registered PD-1 patients number for 14.37% compared to 2008 (table 1).

Comparatively to the other countries, the consumption level of insulin preparations in Ukraine is very low. For instance, the total volume of consumption in France, Germany, Great Britain, Australia is 13.84, 29.15, 19.09, 17.4 DDDS/1000 persons/day, correspondingly [10]. In Lithuania it was 8.5 DDDS/1000 persons/day in 2008, in Norway – 18.87 and 18.88 DDDS/1000 persons/day in 2008 and 2012 correspondingly, compared to 4.86 и 3.44 DDDS/1000 persons/day in Ukraine within the same periods (table 1) [11, 12].

At comparison of consumption data with the disease rate in Ukraine, it has been determined, that provision of PD-1 patients with insulin preparations, not considering their application for treatment of PD-2 patients, has been 289.68 days of treatment per year per one patient in 2012. In terms of the registered PD-1 patient number, 79.61% of them are provided with 1 DDD of total insulin

daily. The obtained data show the non-conformance of consumption volume to the incidence. Besides, the real provision of insulin medicaments is much lower, as far as calculations do not consider data as of insulin-taking PD-2 patients, though their incompleteness due to the on-going formation of actual register of PD patients in Ukraine. The rate of insulin consumption within 2008-2012 in terms of DDDS/1000 persons/day is given in the table 1.

In 2012, A10A C (IADA) and A10A B (SAI и USAI) groups took the lead in the insulin consumption structure as of the total consumption volume, with the rate of 37.21% and 34.88%, correspondingly. The rate of A10A D group (mixture of SAI and neutral protamine hagedorn, mixture of USAI and neutral protamine hagedorn) is 25.29%. Rather a small consumption volume is registered for A10A E group – 2.82%.

A group of prandial insulin (A10A B), used for control of postprandial blood glucose (PBG), is represented with USAI and SAI. The total volume of their consumption was at the level of 1.76 and 1.20 DDDS/1000 persons/day in years 2008 and 2012, which was much lower than in Norway, for instance, for the same periods (6.82 and 7.22 DDDS/1000 persons/day correspondingly) [12]. SAI took the lead in A10A B group with the rate of 96.02 and 91.67%, correspondingly in 2008 and 2012. In absolute terms, their consumption rate was 1.69 DDDS/1000 persons/day in year 2008, and went down for 34.91% to 1.10 DDDS/1000 persons/day in 2012. There was a slight increase (from 2.98% to 9.01%) of their rate in A10A B group of USAI. Their consumption rate increased from 0.065 in 2008 to 0.096 DDDS/1000 persons/day in year 2012. To put this in perspective, the data of 2008 illustrates that the consumption rate of SAI group in Lithuania takes about 9%, and consumption rate of ISAI group – insulin asparagine, insulin glusilin, insulin lispro – is 49%, 27% and 15% respectively. We should mention a substantial reduction of pig insulin consumption (for 95.83%) in 2012 compared to 2008 (from 0.05 to 0.002 DDDS/1000 persons/day). The rate of Ukrainian insulin has reduced for 15.25% compared to the initial period. This way, the carried out structural analysis of insulin, applied for PBG control, evidences low USAI consumption, compared to SAI.

In comparative aspect, USAI have optimal pharmaco-kinetical profile, out of prandial insulin group, corresponding to endogenous peak insulin secretion of a healthy human. As opposed to SAI they start quickly, provide concordance of blood insulin concentration peaks with PBG peak, and have more active elimination, avoiding the layover effect, and thus preventing development of hypoglycemic state. Human engineered SAI is of its best effect only after suction of the most part of carbohydrates after meals, and this way, insulin effect reaches the hyperglycemia, which has already emerged. Besides, insulin level in plasma is still high for up to 6 hours, which increases risk of hyperglycemia development before next meals. Considerable variability of daily insulin action profiles has been also recorded at SAI, with differences in peak concentration of up to 20-30%, which makes individual selection of effective preparation dose more difficult [1,4]. The listed parameters significantly reduce effectiveness of SAI as of PBG control.

We should mention, that PBG control is an important component of cardiovascular pathology progress prevention, as far as fast and great increase of blood glucose indices after meals, and not fasting glycemia, are a direct factor for formation of endothelial dysfunction, atherosclerosis progression and diabetes complication. PBG control together with fasting glycemia and HbA1 is recommended for PD treatment as an important index, reflecting the state of metabolic control [1,4]. Obviously, prevailing application of SAI in Ukraine can be grounded with the price factor. 1 DDD SAI costs 0.41 to 0.58, while USAI costs 1.15 to 1.48 € per 1 DDD. Putting this in perspective, in the Netherlands, Sweden, Great Britain 1 DDD USAI costs less – that is 0.95 to 1.12 €. The given data justifies the availability of SAI. IADA group has shown the greatest consumption volume among insulin preparations, applied for substitutive basal insulin therapy (A10A C (IADA) and A10A D (LAI) group) within the period under study. Its rate in the group of basal insulin preparations is 92.55% and 92.97%, and in absolute terms, it is 1.96 and 1.28 DDDS/1000 persons/day, as of 2008 and 2012 correspondingly. Compared to 2008, there was a reduction of this group consumption for 34.69% in 2012.



Within the structure of IADA consumption, the same way as with SAI consumption data, consumption of pig insulin has been greatly (for 90.38%) reduced compared to year 2008, and domestic insulin consumption remains unchanged (65.31% in 2008 and 62.11% in 2012). Further to the data of 2012, two medicinal preparations – Protafan® HM, (Denmark) and Farnasulin® H NP, (Ukraine) with consumption volume 0.44 and 0.51 DDDS/1000 persons/day are leading as of consumption in IADA group. The rate of LAI among basal insulin preparations is small and equals 7.45% based on the results of year 2008, 7.03% based on the results of year 2012, in absolute terms – 0.158 and 0.097 DDDS/1000 persons/day correspondingly. Insulin glargin has considerable consumption volume (0.09 DDDS/1000 persons/day in year 2008 and 0.073 DDDS/1000 persons/day in 2012) within the period of the study. For comparison, rate of LAI in the group of basal insulin preparations was 31.52% in Norway in 2008, 20.67% and 70.81% in Norway and Lithuania correspondingly, in 2008 [11,12].

Among insulin preparations, applied for substitutive basal insulin therapy, preparations of non-peak action - LAI (insulin glargin and insulin detemir) provide more reliable glycemic control, without regard to meals and while asleep. They imitate rather even (smooth) basal insulin secretion, are less variable, have almost a day long action (20-24 hours) and provide a clinically significant and comparative reduction of glycemia level at the same low risk of hypoglycemia development [2]. The most widely used IADA group provides for a multiple-dose introduction of the preparation within one day, coordination of injections with meals and physical loads, regular glycemia control. These restrictions negatively affect the life quality, often resulting in breach of the therapy mode and do not provide a relatively even level of basal insulinemia day long, thus enhancing the likelihood of hyperglycemia occurrence. Multiple researches, where LAI and neutral protamine hagedorn therapy are compared at their consistent glycemia level control, show LAI as having a better safety profile (as of reduction of hyperglycemia risk – acute, night, registered) [2,3].

At consideration of basal insulin preparation price in Ukraine, cost of 1 DDD IADA equals 0.41 to 0.82 €, the price of LAI is within the range of 1.89 to 2.38 € per 1 DDD. To put this in perspective, 1 DDD LAI in the Netherlands, Sweden and Great Britain costs 1.48 to 1.65 € [8].

A10A D01 preparations (mixtures of SAI and neutral protamine hagedorn insulin preparations) have the greatest consumption volume in the structure of 2-exponential insulin preparations group – 96.94% in 2008 and 97.21% in 2012. The national preparations take leading positions as of the consumption volume, based on the results of the period of research (table 1). The rate of A10A D04 - D05 group preparations consumption (mixtures of USAI and neutral protamine hagedorn insulin preparations) is not significant, their cost is 2 times higher – from 1.15 to 1.32 € per 1 DDD, compared to 0.41 – 0.58 € per 1 DDD for A10A D01 group.

This way, the evaluation of insulin preparations' consumption in the pharmaceutical market of Ukraine within the five years has shown that the consumption structure has remained almost unchanged. The preparations of human insulin - SAI and IADA, mixtures of SAI and IADA, have the highest consumption level (92.63% in 2008 and 93.43% in 2012). Preparations, which are analogous to human insulin - USAI and LAI, are used in small volume (5.21% in 2008 and 6.11% in year 2012). A slight amount of pig insulin consumption was equal to 18% in 2005, it went down to 2.16% in 2008 and to 0.2% in 2012, and in general it reflected the contemporary tendencies as of consumption of preparations of this group.

An increase of expensive analogues of insulin, reduction of human insulin consumption and great reduction of consumption of insulin of animal origin can be seen in the international market of insulin consumption. As of year 2009, less than 25 % of the countries in the world took a small amount of insulin preparations of animal origin. This way, the rate of insulin preparations of animal origin equals 0.7% compared to 2.9% in year 2000, analogues of insulin – 76.15% in 2008 compared to 10.7% in 2000 and human insulin – 23.2% in 2008 compared to 86.3% in 2000. The consumption structure of Lithuania does not contain data of insulin preparations of animal origin as of 2008, human insulin and analogues of insulin take 11.48% and 88.52% correspondingly. The rate of analogues of insulin in Denmark was 61.63% of all the insulin preparations in 2009 [7,9].

We should say that the structure of insulin world consumption market is not even and is characterized with three branches. For countries with high income level, insulin analogues compose two thirds of all the insulin preparations consumed, human insulin preparations – one third. Human insulin preparations take two thirds of all the consumed insulin preparations in countries with average income level. Consumption rate of this insulin group has been reduced in countries with low income level, however this group still has a substantial part in consumption structure (over 90% of all the insulin preparations). Globally, there are two aspects of insulin analogues consumption restraint, which are as follows: no strong proves of their advantages as of HbA1c control and the world economic crisis. Meanwhile, increase of insulin analogues consumption is based not only on certain benefits, but also on active marketing strategy of insulin manufacturers [9].

According to estimates of International insulin fund (IIF), human insulin prevail in consumption structure at its corresponding application is quite reasonable and

acceptable for countries with limited resources of health protection. The main priorities of analogous insulin preparations, compared to human insulin, are: lower frequency of hypoglycemic states, usability, improvement of treatment compliance and improvement of life quality. Together with this, there are evidences (data of meta-analyses, systematic review) that there are no significant difference between them as of provision and support of HbA1c objective values [14-16]. On that basis, some countries review and limit compensations for some categories of patients as of these analogous insulin preparations [6,13]. Experts also consider that certain advantages of insulin analogues level out with no self-control means. That is why, using of limited resources to provide all the patients with human insulin preparations and to take measures, resulting in improvement of their results (training programs, procurement of self-control appliances, test-stripes and monitoring of glycemic control), is more feasible in countries with difficult economic situation.

Insufficient consumption of contemporary analogues of human insulin can be grounded not only with the limited state financing in Ukraine, but with their relatively high practice cost, compared to most countries. This way, comparatively to referent countries (main ones – Albania, Bulgaria, Turkey, Moldova, Russia, Romania and reserve ones – Hungary, Latvia, Lithuania, Czech Republic, Poland) price for insulin preparations in Ukraine differs for 17.02% - 139.08%. For example, compared to minimum price in Turkey, price of Insulin glusilin (Apidra®, Sanofi) is higher for 139.08% in Ukraine, price for insulin lispro as a compound of 2-exponential insulin (Apidra®, Sanofi), compared with a minimum price in Romania is 67.08% higher [5]. In addition, the bidding system for insulin preparations procurement, existing in Ukraine, limits the ability to change insulin therapy rapidly as per the indications, and results in irrational application of financial resources. Potentially, implementation of the program on referent prices for insulin products, which has been announced by the Ministry of health protection of Ukraine, will result in increase of provision ratio level of PD patients with analogous insulin preparations. This way, creation of due structure of insulin preparations consumption in Ukraine (increase of rate of preparations, providing proper treatment of PD patients) is to be performed at existence of evidence base as of their clinical effectiveness, evidences of economic feasibility, based on pharmaco-economic expertise and with application of referent price formation mechanism for all the preparations of the state compensation program.

Conclusions:

- rate of insulin preparations consumption by PD-1 patients, without consideration of preparations for PD-2 patients, evidence the inconsistency of the consumption volume with PD-1 case rate.
- now human insulin preparations have the highest consumption level as opposed to developed countries with high level of analogous insulin consumption;
- application of contemporary highly effective preparations of human insulin analogues (ultra-short and long acting insulin) is insufficient;
- consumption of insulin preparations in Ukraine, in terms of DDDS/1000 persons/day, compared to some European countries, is very low;
- the total consumption volume has been reduced for 29.65% in 2012 compared to year 2008;
- a necessity of pharmaco-economic expertise before introduction of any preparation to the program of state refunding has been determined.

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Table 1. Dynamics of insulin consumption within years 2008-2012 in terms of DDDS/1000 persons/day.

ATC code	Insulin type	Trade name	DDDS/1000 persons/day		Δ,%
			2008	2012	
1		2	3	4	5
Group of prandial insulin - A10A B					
A10A B01, A10A B03 short acting	Engineered human insulin	Actrapid® HM Penfill® (Denmark)	0,48	0,45	- 6,25
		Gensulin P. Bioton (Poland)	-	0,005	-
		Insuman® Rapid. Sanofi (France)		0,01	-
		Farmasulin® H. Farmak (Ukraine)	0,55	0,37	- 32,73
		Humadar® P100P. Indar (Ukraine)	0,57	0,24	- 57,89
		Humulin® Regular. Eli Lilly (USA)	0,04	0,02	- 50,0
		Total: abs. / % of the consumption volume in A10A B01. A10A B03 group	1,64 / 97,04	1,10 / 99,82	- 67,07
	Pig insulin	Monodar®. Indar (Ukraine)	0,05 / 2,96	0,002 / 0,18	- 95,83
Total consumption in A10A B01, A10A B03 group : abs. / %			1,69 / 100	1,102 / 100	- 34,91
A10A B04, A10A B05, A10A B06 ultra-short acting	Insulin lispro	Humalog®. Eli Lilly (USA)	0,005	0,005	-
	Insulin asparagin	Novorapid® Flexpen®. Novo Nordisk (Denmark)	0,06	0,055	- 8,33
	Insulin glusilin	Apidra®. Sanofi (France)	-	0,036	-
	Total consumption in A10A B04, B05, B06 group : abs. / %			0,065 / 100	0,096 / 100
Total in A10A B group: abs/ % of the total volume of all insulin consumption			1,76 / 36,21	1,20 / 34,88	- 31,82
Group of basal insulin - A10A C					
A10A C01, A10A C03 action of average duration and analogues	Human insulin	Gensulin H, Bioton (Poland)	-	0,009	-
		Insuman® Basal, Sanofi (France)	-	0,017	-
		Protafan® HM, Novo Nordisk (Denmark)	0,65	0,44	- 32,31
		Farmasulin® H NP, Farmak (Ukraine)	0,69	0,51	- 26,08
		Humadar® B100P, Indar (Ukraine)	0,54	0,28	- 48,15
		Humulin® НПХ, Eli Lilly (USA)	0,032	0,021	- 34,38
		Total in group: abs. / % of the consumption volume in A10A C01, A10A C03 group	1,91 / 97,45	1,27 / 99,22	- 66,49
	Pig insulin	Monodar® Б, Indar (Ukraine)	0,052 / 2,55	0,005 / 0,78	- 90,38
Total consumption in A10A C group: abs. / %			1,96 / 100	1,28 / 100	- 34,69
Total in A10A C group: abs/ % of the total volume of all insulin consumption			1,96 / 40,33	1,28 / 37,21	- 34,69
Group of basal insulin - A10A E					
A10A E04, A10A E05 long acting	Insulin glargin	Lantus®. Sanofi (France)	0,09	0,073	- 18,89
	Insulin detemir	Levemir® FlexPen® (Denmark)	0,068	0,024	- 64,71
Total in A10A E group: abs / % of the total volume of all insulin consumption			0,158 / 3,25	0,097 / 2,82	- 38,61
Total in group of basal insulin (A10A C and A10A E): abs/ % of the total volume of all insulin consumption			2,12 / 43,62	1,38 / 40,12	- 65,09
Group of 2-exponential insulin - A10A D					
A10A D01, Mixture of short acting and neutral protamine hagedorn insulin	2-exponential Engineered human insulin	Insumal® COMB 25, Sanofi (France)	-	0,027	-
		Mixtard® 30 HM, Novo Nordisk (Denmark)	0,12	0,04	- 65,0
		Farmasulin® H 30/70, Farmak (Ukraine)	0,34	0,48	- 29,17
		Humadar® K25, Indar (Ukraine)	0,48	0,29	- 30,58
		Humulin® M3, Eli Lilly (USA)	0,013	0,004	- 69,23
	Total in group A10A D01: abs. / % of the Consumption volume in A10A D group			0,95 / 99,94	0,84 / 97,67
A10A D04, A10A D05 Mixture of ultra-short acting and neutral protamine hagedorn insulin	Insulin lispro	Humalog® MIX 50, Eli Lilly (USA)	-	0,004	-
	Insulin asparagin	NovoMix® 30 Flexpen® (Denmark)	0,03	0,02	-33,33
	Total in group: abs. / % of the consumption volume in A10A D group			0,03 / 3,06	0,02 / 2,33
Total consumption in A10A D group: abs. / %			0,98 / 100	0,024 / 100	- 40,0
Total in A10A D group: abs/ % of the total volume of all insulin consumption			0,98 / 20,16	0,86 / 25,00	- 12,24
Total, general consumption of insulin preparations: abs/ %			4,86 / 100	3,44 / 100	29,22

Δ - spread of consumption volume (percentage) within the period under study.