Original article

PHARMACOKINETIC AND PHARMACODYNAMIC MODELLING OF BASE INSULINS AND ANALOGS

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Pharmacokinetic modeling implies establishing the medicine dosage regime based on the anticipated course of the effect, depending on the given time. It is based on measuring possible pharmacodynamic parameters that correlate with pharmacokinetic data.

Taking into consideration the latest discoveries on the pharmacokinetics of the base insulins and analogs, the primary aim of this paper was to compare the variability of their pharmacokinetic profile by using therapy monitoring in the patients suffering from the secondary insulin-dependent diabetes mellitus, type II. The secondary aims were: examining the influence of obesity, age and sex onto the pharmacokinetics (PK) of the applied insulins, and comparing therapeutic efficiency of the examined insulin analogs with NPH insulin.

The research was performed at the Endocrinology Clinic, Clinical Center Nis, and it involved 60 patients suffering from the secondary insulin-dependent diabetes mellitus, type II.

The patients were on therapy including the use of NPH insulins for more than a year. All the patients were divided into two therapy groups, with the previous suspension of the insulin therapy:30 patients on therapy including the use of "glargine" insulin and 30 patients on therapy including the use of "detemir" insulin.

By means of pharmacokinetic-pharmacodynamic analog estimation in this research, after three months, a statistically significant pharmacodynamic (PD) effect was obtained, in the sense of a significant drop in the glycemia and glycolized hemoglobin value. *Acta Medica Medianae 2008;47(4):15-19.*

***Key words**: pharmacokinetic, pharmacodynamic, modelling, NPH insulin, detemir, insulin, glargine*

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Introduction

Pharmacokinetic modeling implies establishing the medicine dosage regime based on the anticipated course of the effect, depending on the given time. Pharmacokinetic-pharmacodynamic modeling has been introduced into the use due to an individual variability in effects, for the medicine concentration in plasma does not always correlate with the effects. When it comes to direct effects and fast medicine mechanisms, modeling is simple. It is based on measuring possible pharmacodynamic parameters that correlate with pharmacokinetic data.

In order to achieve normoglycemia and the reduction of possible complications, intensified insulin therapy becomes an optimal way in treating diabetes mellitus, type 2. Insulin therapy can be combined with oral anti-diabetics so as to reduce the dosage of the applied insulin and to avoid the increase of patients` body weight. Even though traditional insulin remedies have a limited use and application, discovering new, long-term effective, base insulin analogs, such as "glargine" insulin and "detemir" insulin, the improvement of pharmacokinetic and pharmacodynamic insulin profile in relation to NPH insulin (neutral protamin Hagedorn insulin) has been made possible. In this way, higher efficiency, safety and variability of the glycemia control is provided (1).

Insulin analogs are monomer insulins whose application kinetics is more optimal than that of the corresponding human insulin remedies. The human insulin analogs have been developed in order to be brought closer to the physiological insulin secretion. Three quick-effect and two base insulin analogs are currently used in clinical practice. "Glargine" insulin is the first basal analog approved for the clinical use and after the application it shows a faster regulation of the glycemia control and a lower risk from hypo glycemia in relation to NPH insulin (2).

The advantages of using "glargine" insulin and "detemir" insulin in relation to the application of NPH insulin are: faster attaining of lower glycemia level, a reduced risk from nightly hypo glycemia and a reduced variability of glucose level in the blood. "Glargine" and "detemir" differ

according to the beginning and the length of the effect itself. In most cases, "detemir" has to be applied twice a day with the patients suffering from DM type 1, and in a very high percentage in the therapy of patients suffering from DM type 2, whereas "glargine" insulin is applied only once a day. Although they display individual pharmacokinetic and pharmacodynamic profiles, "glargine" and "detemir" exert their effect in the same way: by lowering the level of glycocaemia in the blood and by reducing the level of glycolized Hb A1C (3).

Variable values of pharmacokinetic parameters may be brought about by a variety of factors (physiological, pathological and external ones, by interactions of medicaments and nonlinear pharmacokinetics) that need to be taken into consideration upon the occasion of individual adaptation of the medicine dosage regime. Even in that case, there are frequently enough reasons left for variability, so that, with the purpose of conducting a rational pharmacotherapy, pharmacokinetic- pharmacodynamic modeling is introduced.

Aims

Taking into consideration the latest discoveries on the pharmacokinetics of the base insulins and analogs, the primary aim of this paper was to compare the variability of their pharmacokinetic profile by using therapy monitoring in the patients suffering from the secondary insulin-dependant diabetes mellitus, type II. The secondary aims were: examining the influence of obesity, age and sex onto the pharmacokinetics (PK) of the applied insulins and comparing therapeutic efficiency of the examined insulin analogs in relation to the NPH insulin.

Material and methods

In this study, a retrospective and comparative method for clinical research was used. The research was performed at the Endocrinology Clinic, Clinical Center Nis and it involved 60 secondary insulin dependent patients with a diagnosed diabetes mellitus, type 2.

- The patients were on therapy including the use of NPH insulins for longer than a year. After anamnestic, clinical and laboratory testing, all the patients were divided into two therapy groups, with the previous suspension of the insulin therapy: I group - 30 patients on therapy including the use of "glargine" insulin,
- II group - 30 patients on therapy including the use of "detemir" insulin.

All the patients had had their anthropometric parameters (height, weight) determined at the beginning of testing, as well as their body mass index (BMI).

Insulin dosages were determined individually, depending on the glycemia level and the value of glycamised hemoglobin A1c (ranging from 16 to 32 i.j. insulin analogs).

Estimating pharmacodynamic effect also implied therapy monitoring (determining and observing the glycoregulation, glycemia and glycolized hemoglobin control parameters) in a patient's morning blood sample.

Laboratory testing included:

- glycemia control and determining of HbA1c before the use of analogs,
- glycemia control after using the analogs for a month, and
- glycemia control and HbA1c after using the analogs for three months.

The obtained data was classified, and the data schedule together with the graph chart was made. The results were processed and displayed according to the descriptive statistical methodology. For testing the results parametric statistical tests were used, primarily the Student's t- test. Differences on the level of $p<0.05$*, $p<0.01$** were taken as statistically significant.

By means of pharmacokinetic-pharmacodynamic analog estimation in this research, after three months, a statistically significant pharmacodynamic effect was obtained, in the sense of a significant drop in the glycemia and glycolized hemoglobin value.

Results

General characteristics of the examined patients suffering from diabetes mellitus in the therapy including the use of NPH insulins are shown in the Table 1.

Performed statistical analysis did not show more significant differences in the incidence of patients among sexes. The average duration of diabetes mellitus and the patients' age did not differ significantly between the patients of male and female sex. The examined men were significantly taller and of greater body weight than women ($p<0.01$), but the obesity level expressed through BMI did not differ significantly between the sexes (Table 1).

The general characteristics of the examined patients on various therapy regimes of insulin analogs are shown in Table 2.

Table 1. General characteristics of the examined patients

Number (%)	Women	Men	Total
	38 (63%)	22 (37%)	60 (100%)
Age	58.07±12.08	57.9±13.05	58.01±12.34
Duration of illness (months)	114.57±75.32	133.2±80	121.4±76.95
Height (cm)	160.84±6.2	171.9±6.3**	164.9±8.2
Weight (kg)	69.39±13.2	79±12.58**	72.91±13.7
BMI (kg/m^2)	26.7±4.9	26.31±3.1	26.56±4.33

$p<0.01$**

Table 2. General characteristics of the examined patients on insulin analogs therapy

	Glargine	Detemir	total
Women (%)	19 (50%)	19 (50%)	38 (100%)
Men (%)	11 (50%)	11 (50%)	22 (100%)
Age	60.9±10.4*	55.13±13.58	58.01±12.34
Duration of illness (months)	147.56±91.07**	95.26±48.35	121.41±76.95
Height (cm)	163.76±7.38	166.03±8.9	164.9±8.2
Weight (kg)	74.2±10.59	71.63±16.31	72.91±13.7
BMI (kg/m^2)	27.6±3.83*	25.53±4.62	26.56±4.33

p<0.05 *, p<0.01 **

Table 3. Influence of obesity, sex and age onto the pharmacokinetics of the applied insulin and insulin analogs

BMI (kg/m^2)	Glycemic values (mmol/l)		HbA1c values (%)		% reductions HbA1c
	NPH	analog	NPH	analog	
<20	9.93±4.22	7.1±1.99	9.06±0.89**	7.73±1.19	1.33
20-25	9.9±2.2**	7.27±1.04	9.41±1.3**	7.64±0.74	1.77
26-30	9.6±1.8**	6.89±1.09	9.07±1**	7.46±0.94	1.61
>30	11.05±2.66**	7.43±0.78	10.65±1.9**	8.3±1.07	2.35

p<0.01**

Table 4. Observing PK and PD effect of the applied insulins and analogs in relation to sex

sex	Glycemic values (mmol/l)		HbA1c values (%)	
	NPH	analog	NPH	analog
men	9.62±1.7	7.01±1.22**	9.29±1.18	7.53±0.94**
women	10.17±2.44	7.2±0.99**	9.5±1.44	7.73±0.89**

p<0.01**

Table 5. Observation of PK and PD effects of the applied insulins and analogs in relation to patients' age

Age(years)	Glycemic value (mmol/l)		HbA1c value (%)	
	NPH	analog	NPH	analog
<65	9.81±2.23**	7.14±0.97	9.41±1.42**	7.65±0.92
>65	10.37±2.19**	7.11±1.33	9.46±1.16**	7.67±0.91

p<0.01**

The patients who were treated by "glargine" insulin were significantly older (p<0.05), with longer duration of diabetes mellitus and a higher obesity level (p<0.01) in relation to the patients who were given "detemir." The other examined parameters did not differ significantly between the groups (Table 2).

The influence of obesity on PK characteristics and pharmacodynamic response of both applied analogs and NPH insulins is shown in Table 3.

Table 3. Influence of obesity, sex and age onto the pharmacokinetics of the applied insulin and insulin analogs.

The results showed that the increase of the obesity level leads to the deterioration of glycol-regulation, on the occasion in which the application of insulin analog after the period of three months led to a significant reduction of morning glycemia value and glycosed hemoglobin in relation to the therapy based on the use of NPH insulins (p<0.01).

The reduction of the glycemia value and HbA1c is marked both in normally weighted and obese patients (Table 3).

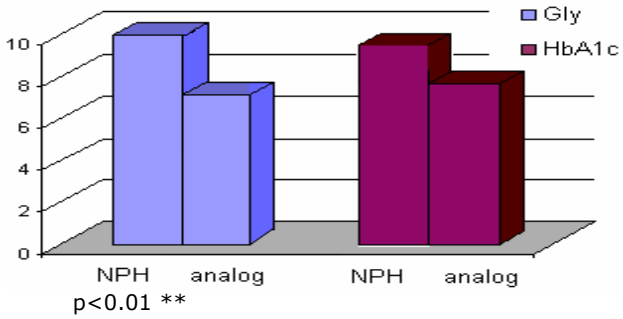
The influence of sex of the examined patients onto PK and PD effect of the applied insulins and insulin analogs is shown in Table 4.

No significant difference was registered in the display of PK characteristics and pharmacodynamic response between NPH insulin and analog in relation to sex. The application of an insulin analog lead to a significant reduction of glycemia and HbA1c after three months of use in the patients of both sexes (p<0.01) (Table 4).

Observing the influence of older age onto PK and PD effects of the applied insulin analogs is shown in Table 5.

By examining the influence of older age onto a pharmacokinetic profile and a pharmacodynamic effect of NPH insulin and analogs, no significant difference was registered. The application of insulin analogs in a three-month period lead to a significant glycemia and the glycolized hemoglobin value reduction in the patients both younger and older than 65 (p<0.01) (Table 5).

From Graph 1, a conclusion can be drawn that the values of glycemia were, statistically speaking, significantly lower by 28.19%, whereas the lowering of the glycolized hemoglobin was 16.6% after the three-month application of insulin analogs.



Graph 1. Glycemia and glycolized hemoglobin value with the applied insulins

Discussion

The benefit of glycemia control with the purpose of reducing the risk of microvascular complications in the patients suffering from diabetes type 1 and 2 (DM type 2) is nowadays confirmed by a few major studies (4).

A few factors significantly restrict the normalization of the glycemia level in the patients suffering from diabetes mellitus. They are conjoint with hyper-glycemia, side-effects of the medicaments, contraindications when applying certain medicaments (renal dysfunction, heart insufficiency), the risk of hypo-glycemia and the mutual influence of the glycemia control and the increase of body weight (5). Oral anti-diabetics are applied in the therapy of diabetes mellitus in order to retain the aimed glycemia level in a short period of time. However, the progressive nature of DM type 2 in most cases requires the combination of more oral remedies, whereas the long-term control of glycemia is most frequently achieved by applying insulin therapy. The degree of reliability and safety often restricts the optimal application of anti-diabetics like derivates of sulfonilurea and thiazolidinedione (6).

The insulin treatment is undoubtedly induced in a patient suffering from DM type 2 in whom there is a marked insulin deficit. The treatment is considered to be successful if the applied therapy leads to the regulation of diabetes throughout a longer period of time. The aims of diabetes therapy are: achieving normoglycemia or approximate normoglycemia, hypertension prevention or control, the regulation of hyperlipidaemia and preventing vascular complications (7).

The conducted research showed that the increase in the degree of obesity deteriorates the glycol-regulation in the patients suffering from diabetes mellitus. After the three-month application of the insulin analog, it comes to a significant reduction of glycemia and glycolized hemoglobin in relation to the initial therapy by means of NPH insulins ($p<0.01$) (Table 3). The base insulin supplementation does not induce a significant increase in body weight. The dosage of insulin must be primarily adjusted to morning glycemia, and it is corrected according to the degree of obesity as the most significant clinical marker of insulin resistence (8).

Introducing DM type 2 insulin into the therapy, a new dimension in treating these patients is obtained. By means of pharmacokinetic-pharmacodynamic analog estimation in this research, after three months, a statistically significant pharmacodynamic effect was obtained, in the sense of a significant drop in the glycemia and glycolized hemoglobin value ($p<0.01$) (Graph 1). Our results are in keeping with a numerous bibliographical data (3,4,8). Clinical experiences that included the application of insulin analog in treating DM type 2 showed a superior effect and better tolerance. After going through the bibliography, it can be concluded that certain authors determined a lower incidence of symptomatic hypoglycemia in the group of patients treated by means of insulin analogs in relation to the patients treated by NPH insulin (9).

The incidence of nightly hypoglycemia in the patients on analogs was lower in the majority of the presented studies (4,8,9). Moreover, it was shown that "glargine" insulin provides a better glycemia control and that it is related to a lower risk from hypoglycemia in the patients suffering from type 2 diabetes mellitus who had been previously treated by means of oral hypoglycemics, the combination of oral hypoglycemics and NPH insulin, or only by means of base insulin (NPH) insulin, or cordon insulin (10). The three-moth therapy monitoring with the insulin analogs (glargine and detemir) has determined a significant glycemia and glycolized hemoglobin reduction in relation to the initial therapy by means of NPH insulins. glycemia values in the course of analog application were lowered by 28.19 %. The reduction of glycolized hemoglobin was 1.56 % which is in keeping with the values obtained in the study by Rosenstock et al. (11).

"Glargine" insulin provides the equivalent glycemia control in relation to NPH insulin, and it is conjoint with the reduced percent of hypo glycemia, especially nightly ones, owing to its twenty-four hour profile of effect and performance (12).

"Detemir" insulin is a new insulin analog, superior in relation to NPH insulin. This insulin analog shows a shorter activity period in relation to "glargine" insulin (13).

One way of postponing and reducing complications with diabetes mellitus is keeping a permanent normoglycemia with reduced inflammation and oxidative stress (14) in adults, children and adolescents (15). Bibliographic data show that long-term analogs such as "glargine" and "detemir" provide a lower risk from hypo glycemia and they improve the glycemia control (9). Aggressive dosage oscillations of "glargine' and "detemir", make it easier to achieve the aimed glycemia levels. The success of good glycemia control with the low risk of hypoglycemia development is made possible by a simple application of base insulin analogs (16).

Conclusion

Insulin analogs have a significantly better pharmacokinetic profile and pharmacodynamic effect in relation to NPH insulins in obese patients suffering from diabetes mellitus type 2, without any significant difference in pharmacokinetic variability caused by sex and age.

The research results have demonstrated that insulin analogs, by means of their favourable

pharmacokinetics, display a significantly improved therapy effect in relation to NPH insulins.

Owing to the specific pharmacokinetics of insulin analogs which is the closest to the profile of the base insulinisation, the advantage of the same in relation to NPH insulin is determined in the patients suffering from secondary insulin-dependant diabetes mellitus, based on the indirect therapy monitoring.

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FARMAKOKINETIČKO I FAMAKODINAMIČKO MODELIRANJE BAZALNIH INSULINA I ANALOGA

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Farmakokinetičko modeliranje podrazumeva postavljanje režima doziranja lekova na osnovu predviđanja toka efekta u zavisnosti od vremena. Zasniva se na merenju mogućih farmakodinamičkih parametara koji korelišu sa farmakokinetičkim podacima.

Imajući u vidu najnovija saznanja o farmakokinetici bazalnih insulina i analoga, cilj rada bio je upoređivanje varijabilnosti njihovog farmakokinetičkog profila korišćenjem indirektnog terapijskog monitoringa, kod bolesnika sa sekundarno insulin zavisnim dijabetes meltusom tip II. Pored toga, ispitivan je uticaj gojaznosti, životnog doba i pola na farmakokinetiku (FK) primenjenih insulina i upoređivana terapijska efikasnost ispitivanih insulinskih analoga u odnosu na NPH insulin.

Ispitivanje je obavljeno na Klinici za endokrinologiju Kliničkog centra u Nišu i obuhvatalo je 60 bolesnika sa dijagnostikovanim dijabetes melitusom tip 2, sekundarno insulin zavisni.

Bolesnici su bili na terapiji NPH insulina duže od jedne godine. Nakon anamnestičkog, kliničkog i laboratorijskog ispitivanja, svi bolesnici su podeljeni u dve terapijske grupe, uz prethodnu obustavu insulinske terapije. Prva grupa obuhvata 30 bolesnika na terapiji insulinom glargine, a druga 30 bolesnika na terapiji insulinom detemir.

Rezultati ispitivanja su pokazali da analozi insulina, zahvaljujući povoljnoj farmakokinetici ispoljavaju značajno bolji terapijski efekat u odnosu na NPH insuline. *Acta Medica Medianae 2009;48(1):15-19.*

Ključne reči: *farmakokinetičko-farmakodinamičko modeliranje, NPH insulin, bazalni insulinski analozi, insulin glargine, insulin detemir*