diabetes, pharmacokinetic, model, glucose level

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MODEL OF HUMAN SYSTEM OF GLUCOSE LEVEL STABILISATION – SELECTED PROBLEMS OF PARAMETER IDENTIFICATION

The article presents methodology and partial results of research aiming at constructing a model of human system of glucose level stabilization. The article includes: the description of the modeled system, analysis of already applied mathematical models, proposition of a new 3-compartment model and partial results of the model identification. The proposed model is a non-linear one. It constitutes a system of differential equations.

1. INTRODUCTION

Being well-acquainted with processes occurring in the human body after the administration of drugs and understanding these processes better, makes it possible to establish rules for optimal medication administration and dosage. The analysis of concentration-time profiles of ksenobiotics in the human body and body reaction-time profiles constitutes an obvious cognitive tool in this research. Such an analysis can be further used to build and verify mathematical models which reveal dynamics similar to the one observed in the experimental stage as well as to identify the parameters of these models.

This article deals with creating a mathematical model describing some interrelationships in human carbohydrate metabolism. It's aim is two-fold:

- to propose a new 3-compartment model of glucose – insulin– sulphonylurea system,
- to discuss parameter identification of the model and to present partial results of identification.

The proposed model is a non-linear one. It constitutes a system of differential equations.

2. DESCRIPTION OF MODELLED SYSTEM

Mechanisms regulating blood glucose level. Insulin is the most basic factor regulating blood glucose level. It is a peptide hormone produced in pancreatic islet "beta" cells. It is created as a preproprotein. Pre-proinsulin contains a signal peptide after whose cleavage the rest is folded and linked with disulphur bridges as proinsulin. It is composed of three chains, one of which, called C-

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peptide or connecting peptide, is cleaved from the rest before secretion. Both insulin and C-peptide leave the cell. Marking C-peptide has been applied in diagnosing pancreatic islet cells function in releasing insulin. The half-life of this important hormone is about 5 minutes [1].

There are also a few substances in plasma which reveal insulinlike activity, so called non suppressible insulinlike activity (NSILA). These are, among other things, insulinlike growth factors IGF-I and IGF-II. Physiological results of insulin's activity are fairly complex. Their final effects involve concentrating carbohydrates, proteins, and fats. So far research has concentrated on fast activity, which stimulates increased transport of glucose, amino acids and potassium ions into insulin-sensitive cells [7]. When there is a lack of insulin, a small amount of glucose enters the cells in accordance with the gradient of concentration, but it is insulin which significantly increases the speed of glucose transport. It is an example of a facilitated diffusion, with permeated course kinetics in a system of limited availability of the specific carriers called glucose transporters. They are created in cytoplasm and insulin increases their accumulation in the cell membrane. After intravenous administration of insulin, blood glucose level immediately decreases (maximum effect after about 30 minutes). Insulin is a strategic hormone for liver as it facilitates the synthesis of glycogen (storage form) and reduces glucose secretion – slows down the synthesis of enzymes responsible for the process of gluconeogenesis and induces the synthesis of key glicolitical enzymes such as glucokinase.

A normal fasting insulin level for healthy people in venous blood plasma determined by means of a radioimmunological metod equals 0-502 pmol/ (0-70 mikrounits/ml). The amount of insulin secreted during a period of rest is about 7 nmol/h (1 unit/h) while after a meal it is 5-10 times more. The amount of insulin secreted during one day in healthy man amounts to about 287 nmols (40 units). The regulation of insulin secretion operates via a feedback mechanism connected with the glucose level in blood reaching pancreatic islet cells.

Apart from glucose, substances stimulating the secretion of insulin include: amino acids, gastrointestinal hormones, glucagons, cyclical AMP and substances generating cyclical AMP, teophiline, sulfonylureas and others [9].

Glucagon undoubtedly belongs to the group of most important substances besides insulin, important for carbohydrate conversion. It has the opposite (catabolic) role and triggers secretion of glucose, fatty acids, and amino acids from their storage areas into the blood. [6].

3. ANALYSIS OF MATHEMATICAL MODELS APPLIED IN PHARMACEUTICAL RESEARCH

Pharmaceutical research applies, among other things, mathematical models, called pharmacokinetic models, pharmacodynamic models, and pharmacokinetic-pharmacodynamic models [3], [10], [13], [14]. Pharmacokinetic models describe concentration-time profiles of ksenobiotics, taking into consideration the way of administering them, processes of relocation between compartments and their elimination from the human body. An exemplary bi-compartment model depicted in Fig. 1 is described by a system of equations (1).

$$\begin{aligned} \dot{x}^1 &= -(k^{10}+k^{12})x^1 + k^{21}x^2 + u(t) \\ \dot{x}^2 &= k^{12}x^1 - (k^{20}+k^{21})x^2 \end{aligned} \tag{1}$$

where:
x^1 , x^2 – concentration of ksenobiotics in compartment 1 and 2, respectively;
k^{12} , k^{21} – coefficient of ksenobiotics diffusion between compartments 1 and 2, respectively;
k^{10} , k^{20} – coefficient of ksenobiotics dissipation (clearance) in compartment 1 and 2, respectively;
u(t) - an input function representing external ksenobiotics administration.

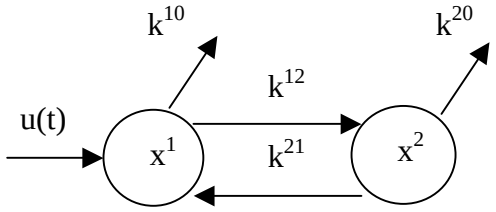

Fig. 1. Schematic diagram of a bi-compartment pharmacokinetic model

Applied input functions u(t) include:
$u(t) = D \cdot \delta(0)$;where δ – Dirac's delta function (quick intravenous injection IV);
$u(t) = D/t_0 \cdot (h(0)-h(t_0))$where h – unit Heaviside's function (short-term injection);
$u(t) = D \cdot k_1 \cdot \exp(-k_1 \cdot t)$ (intra-muscular or oral administration);
D – administered dose of a ksenobiotic

Pharmacodynamic models generally describe the relationship between the concentration of a ksenobiotics and the measurable biological effect (body reaction). Attention should be drawn particularly to Emax model, revealing the desired asymptotic qualities (saturation) [10].

Pharmacokinetic-pharmacodynamic models are inertion models of the 1st order. They have richer modelling possibilities and their application is similar to pharmacodynamic models. More detailed description of these models is given in [4], [8].

4. PROPOSED MODEL

At this point the authors propose a model of glucose influence on insulin secretion from pancreas and insulin influence on glucose absorption by cells, after administering sulphonylurea (Fig. 2). The presented model is a modified version of the model created by one of the co-author [8]. To identify the glucose – insulin – sulphonylurea system, authors assume the structure of a pharmacokinetic model, involving two basic compartments for glucose and sulphonylurea: blood (1) and inter-tissue fluid (2), and for insulin additionally a compartment of tissues (3). The proposed model takes into consideration mutual interaction of ksenobiotics according to the formulas (2), (3).

Subscripts *g, i,* and *t* for *x* variables, *k* parameters, and *u* interactions refer to: g – glucose,

i – insulin, and t - sulphonylurea. Superscripts refer to compartment numbers (e.g. k_g^{12} denotes translocation coefficient of glucose from compartment 1 to 2).

Interaction $u_i(x_g^1, x_t^1)$ refers to insulin secretion by pancreas, which depends on blood glucose and sulphonylurea level. The value of coefficient k_g^{20} depends on the concentration of insulin in the compartment of tissues.

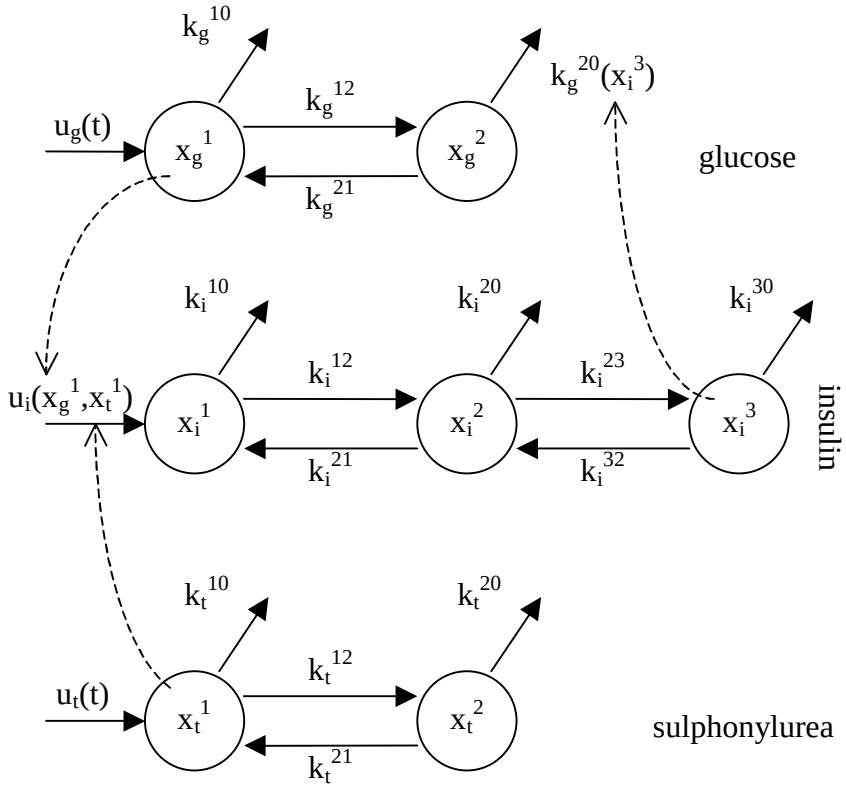

Fig. 2. Schematic diagram of a 3-compartment pharmacokinetic model of glucose – insulin – sulphonylurea system

$$u_i(x_g^1, x_t^1) = \begin{cases} 0 & for \quad d < 0 \\ d & for \quad d \geq 0 \end{cases}$$
$$d = k_g^1 x_g^1 + k_t^1 x_t^1 - h_i^1 \tag{2}$$

$$k_g^{20}(x_i^3) = k_g^2(1 + k_i^2 x_i^3) \tag{3}$$

where:
k_i^1, k_i^2, k_g^1, k_g^2 – parameters; h_i^1 – threshold value; d – auxiliary variable.

In the conducted experiments the author relied on results of measurements of sulphonylurea and glucose levels after administration of 6 doses of sulphonylurea in short three-minute intravenous drips which were available in literature [1], and on the results of analysis of these data presented in paper [4].

Three-compartment pharmacokinetic model of glucose – insulin – sulphonylurea system is of the form (4) (superscripts 1,2,3 denote the compartment numbers). The model is a nonlinear one.

$$\dot{x}_g^1 = -(k_g^{10} + k_g^{12})x_g^1 + k_g^{21} x_g^2 + u_g(t)$$

$$
\begin{aligned}
\dot{x}_g^{\,2} &= kg^{12}x_g^{\,1} - (k_g^{20} + k_g^{21})x_g^{\,2} \\
\dot{x}_i^{\,1} &= -(k_i^{10} + k_i^{12})x_i^{\,1} + k_i^{21}x_i^{\,2} + u_i(t) \\
\dot{x}_i^{\,2} &= k_i^{12}x_i^{\,1} - (k_i^{20} + k_i^{21} + k_i^{23})x_i^{\,2} + k_i^{32}x_i^{\,3} \\
\dot{x}_i^{\,3} &= k_i^{23}x_i^{\,2} - (k_i^{30} + k_i^{32})x_i^{\,3} \\
\dot{x}_s^{\,1} &= -(k_s^{10} + k_s^{12})x_s^{\,1} + k_s^{21}x_s^{\,2} + u_s(t) \\
\dot{x}_s^{\,2} &= k_s^{12}x_s^{\,1} - (k_s^{20} + k_s^{21})x_s^{\,2}
\end{aligned}
\qquad (4)
$$

5. IDENTIFICATION PROBLEM AS A NONLINEAR REGRESSION

The task of the parameter identification of the proposed models – via systems of first order differential equations – is formulated as the minimization of the sum of squared deviations of values of real concentration-time profile from the model's concentration-time profile. This minimum is a non-linear function of the parameters we are looking for. That is why the procedure of minimization is carried out via the Nelder-Mead simplex method – a method for finding a local minimum of a function of several variables. Runge-Kutta 4^{th} and 5^{th} order algorithms have been used for the integration of first order differential equations. The authors used the interpolation procedure with spline functions to obtain function values after integration in appropriate time points. Calculations were conducted in MATLAB environment [16].

Taking advantage of the fact that sulphonylurea concentration in the proposed model does not depend on other ksenobiotics, we have carried out a partial identification of parameters: only in this part of the model which describes sulphonylurea concentration-time profiles [10].

It is a bi-compartment model (see Fig. 1), which is described by the system of equations (1). We introduced two changes into it in the course of identification experiments. We skipped k_t^{20} coefficient and we introduced and additional V^1 parameter referring to the capacity of compartment 1. This parameter is indispensable for calculating concentrations in compartment 1 if a model variable x_t^1 describes momentary amount of sulphonylurea in the compartment.

The identification process consisted in searching for the best possible set of parameters so that concentration-time profiles reflect most accurately real-time profiles, determined for people after administering six different doses of sulphonylurea.Calculations yielded a fairly accurate model.

Table.1 Results of parameter identification in the bi-compartment pharmacokinetic model of tolbutamide concentration-time profiles for humans.

$\Sigma\delta^2$	k^{10}	k^{12}	k^{21}	V^1	$d_0 (+x_t^1)$
3203.9	0.0048	0.0883	0.1341	4.5083	5.942

Additional d_0 parameter results from the search for a potential systematic error in real measurements.

Further research aims at identifying the remaining parameters of the model as well as the model's expansion so as it accounts for the influence of liver and glucagon.

6. SUMMARY

The article proposes a mathematical model of glucose – insulin – sulponylurea system. and presents methodology with partial results of the model parameters identification. The model take into account three compartments: blood, inter-tissue fluid and tissue compartment. The model constitutes the nonlinear system of differential equations of the 1st order. In order to identify parameters some numerical technics has been applied. Results refering to some parameters are given.

Further research will be devoted to identification of the remining parameters.

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