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Computer model of anticoagulation treatment

Abstract. *A number of patients requiring anticoagulation therapy are growing. Experts estimated worldwide number of these patients at seven million, in Europe about two million. Reasons for the use of anticoagulant therapy is not only therapeutic (treatment of blood clots), but also prevention (prevention of formation of blood clots). However the treatment can be followed by serious side-effects caused by an elevated or diminished international normalized ratio (INR). The paper deals with possibilities of computer modelling of pharmacokinetics of warfarin during anticoagulation treatment.*

Streszczenie. *Liczba pacjentów wymagających leczenia przeciwzakrzepowego ciągle wzrasta. Eksperci oceniają, że liczba takich pacjentów na świecie sięga 7 milionów, a w Europie – 2 milionów. Potrzeba leczenia przeciwzakrzepowego wynika nie tylko terapii ale i profilaktyki. Niestety, stosowanie leków przeciwzakrzepowych wiąże się z poważnymi efektami ubocznymi. W artykule opisano numeryczne modelowanie farmakokinetyki Warfarinu stosowanego w czasie leczenia przeciwzakrzepowego. (**Numeryczne modelowanie leczenia przeciwzakrzepowego**).*

Keywords: pharmacokinetics, warfarin, nonlinear model
Słowa kluczowe: farmakokinetyka, Warfarin, model nieliniowy

Introduction

Coagulation is an important part of haemostasis, providing a complex process in which blood forms clots. A damaged blood vessel wall is covered by a platelet and fibrin-containing clot to stop bleeding and begin repair of the damaged part. Disorders of coagulation can lead to an increased risk of bleeding (haemorrhage) or obstructive clotting (thrombosis). Wide group of diseases and clinical conditions resulting in thrombosis requires a treatment with anticoagulants. For instance as a prevention of arterial thrombosis due to atherosclerosis is usually recommended the general principles of healthy living, such as no smoking, exercise, maintaining normal body weight and balanced nutrition. In cases that these recommendations are insufficient an anticoagulation therapy is utilised to prevent development of thrombus. The occurrence of thrombophilic states can be caused by many factors as surgery, trauma, endoprosthesis, long-term hospitalization, plaster fixation (especially lower extremity) and many more.

Warfarin belongs to most widely used coumarin anticoagulants, especially in treatment of atrial fibrillation, hearth valve prosthesis, deep vein thrombosis or pulmonary embolism. However, usage of warfarin can be potentially harmful due to very narrow therapeutic range and very individual range of sensitivity to dose. Inappropriate dosage for more sensitive patients can cause haemorrhagic complication and lead to serious life threating bleeding. Also age, gender, co-administration with drugs and dietary interaction from food containing vitamin K causes difficulties in proper dose assessment. Vitamin K takes an opposite action to warfarin in process of forming coagulation factors. The focus of this paper is on the modelling of warfarin pharmacokinetics and pharmacodynamics.

Warfarin affects synthesis of the vitamin K-dependent coagulation factors II, VII, IX and X. It acts trough the interference with vitamin K cycle in the liver. Warfarin influence leads to secretion of inactive clotting factors. In therapeutic doses, reduces the synthesis of coagulation factors in 30 to 50% and weakens its biological activity. The full effect can be observed within few days (2 to 7), during which are the coagulation factors gradually eliminated from the circulation. Many commonly used medications and foods as well (particularly fresh plant-based foods containing vitamin K) interacts with warfarin. Therefore activity of warfarin has to be monitored by blood testing for the international normalized ratio (INR) to ensure that the taken dose is adequate yet safe. The value of INR is estimated from blood sample as ratio of patient blood sample prothrombin time to normal blood sample prothrombin time (the time within plasma sample forms clot). Too high INR represents a high risk of bleeding, while an INR below the therapeutic border indicates an insufficient protection against thromboembolic events. The risk for major hemorrhage during warfarin cure is associated with INR greater than 4.0 and for the INR below the therapeutic range 2.0 increases the risks for thromboembolism and warfarin resistance. Therefore setting of the proper dose is very important.

Model of warfarin disposition

Warfarin is usually administered by oral and is completely absorbed. After it is absorbed almost all (99%) is bounded to plasma proteins (mainly albumin) and remaining 1% of free warfarin is biologically active in liver. Therein it inhibits vitamin K epoxide reductase (VKOR), which is a key enzyme system for regeneration of reduced vitamin K. This leads to inhibition in forming of functional clotting factors by means of γ-glutamyl carboxylase (GGCX).

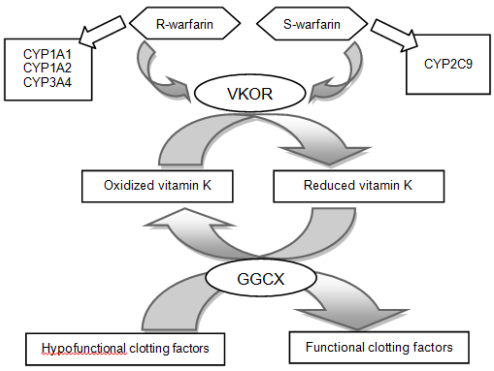

Fig. 1. Pharmacology of warfarin

Warfarin is manufactured as racemic mixture of S- and R- warfarin, where S-warfarin is approximately 3 to 5 times more potent than R-warfarin. S-warfarin is metabolised by the cytochrome p450 2C9 enzyme (CYP2C9) and R-warfarin by other cytochrome p450 enzymes. Primary metabolic enzyme for warfarin is considered CYP2C9. The CYP2C9 gene has more than 30 known variants of alleles and some of them shows lowered enzymatic activity, which can cause higher risk of bleeding. That means the dosing especially in treatment initiation is very individual. Another genetic parameter represents the target of warfarin - VKOR enzyme, which is significantly linked with warfarin sensitivity and the need of higher or lower dose. Lots of literature deals with genotyping in warfarin dosing. For the purpose of this paper a normal S-warfarin metabolism phenotype is chosen.

Pharmacokinetics and pharmacodynamics

Physiologically based pharmacokinetic models describe drug disposition. They characterize the time behaviour of drug concentrations in plasma (blood) and also in important organs and tissues. It can provide information about the role of various physiologic perturbations on these concentrations. Physiologic pharmacokinetic modelling requires actual drug concentration determinations not only in plasma but in appropriate organs and tissues, with the unanalysed tissues lumped into one compartment. [2]

Target-mediated drug disposition represents an assumption that a significant proportion of the drug (relative to dose) is bound with high affinity to a receptor, enzyme, or transporter [3]. The pharmacokinetic model of target-mediated drug disposition is shown on Fig. 2.

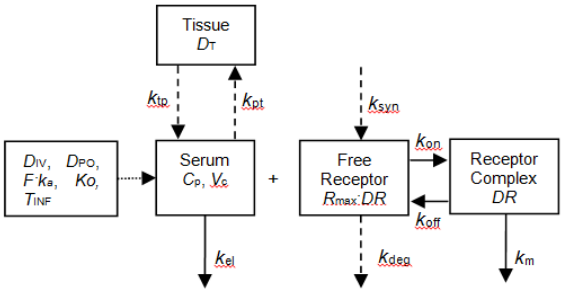

Fig. 2. Pharmacokinetic model of target-mediated drug disposition according to [1]

Central compartment represents drug by concentration C_p and volume V_c. Hence it binds with rate k_{on} to free receptors and forms a drug-receptor complex DR. Total binding capacity represents R_{max}. Created DR can dissociate (rate constant k_{off}) or degrade (rate constant k_m). Unbound drug can be also directly eliminated with rate constant k_{el} or pass to non-specific tissue binding (D_T, k_{pt}, k_{tp}). Tissue compartment and degradation k_m are optional in this type of model.

For description of model following differential equations are used

$$(1)\quad \frac{dC_p}{dt} = C_p(0) - k_{el}C_p - k_{on}\left(R_{\max} - DR\right)C_p + k_{off}DR\,,$$

$$(2)\quad \frac{dDR}{dt} = k_{on}\left(R_{\max} - DR\right)C_p + \left(k_{off} + k_m\right)DR\,,$$

$$(3)\quad \frac{dR_{\max}}{dt} = k_{syn} - k_{\deg}\left(R_{\max} - DR\right)C_p - k_m DR\,,$$

where k_{syn} is production constant and k_{deg} degradation rate of free receptor. Because system is assumed to be stationary can be production rate defined as

$$k_{syn} = k_{\deg}R_{\max}(0)$$

where $R_{max}(0)$ is initial condition of free receptors, the receptor density in absence of drug. Tissue compartment D_T was not included in model.

Computed S-warfarin plasma concentrations is used in evaluation of INR

$$(4)\quad \frac{dINR}{dt} = R_{\max} - INR\left(1 - \frac{I_{\max}C_p}{IC_{50} + C_p}\right),$$

where I_{max} is maximum inhibitory factor and IC_{50} is drug affinity.

Parameters used in model are adopted from literature [1], [4] and are listed in Table 1.

Table 1. The parameters of model

Parameter	Value	Unit
k_{on}	0.1	units^{-1} hr^{-1}
k_{off}	0.1	hr^{-1}
k_{deg}	1	hr^{-1}
k_{el}	$\frac{\ln(2)}{t_{1/2}} = \frac{\ln(2)}{38}$	hr^{-1}
k_m	0.1	hr^{-1}
$R_{max}(0)$	100	units
I_{max}	2.2	-
IC_{50}	1500	units ml^{-1}

Value $t_{1/2}$ represents biological half-life of S-warfarin which varies in different sources. We use value 38 hours. Dose interval is 24 hours. Model and simulation is performed in Matlab environment. Results of simulation are shown on Fig. 3. The value of INR was computed for four values of dose {500, 1000, 1500, 2000 units}. On figure it is grey, dotted, dashed and solid line. The value of INR increases with time and each new dose.

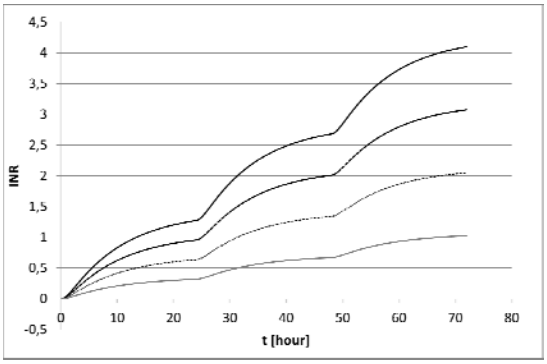

Fig. 3. INR calculated for various doses repeated in 24 hour cycle

Conclusion

Pharmacokinetics – pharmacodynamics model was performed for simulation of warfarin anticoagulation treatment. From target mediated drug disposal model equation (1) to (3) was calculated plasma drug concentration and consecutively used in evaluation of INR using equation (4). Dose interval used in model was 24 hours. Simulations were performed for four values of dose. It is necessary to note that results of simulations have strictly theoretical character and were not compared with any clinic data. Presented model represents first step in development of computer aided system for initiation and maintenance dose evaluation which can help in decision making in more personalised warfarin anticoagulation treatment. Parameters of model can be adjusted according to individual patient genome (CYP2C9, VKORC1). Model will be further developed to consider K vitamin income and some diseases interfering with vitamin K metabolism.

REFERENCES

[1] Mager DE, Jusko WJ., General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinet Pharmacodyn* 28 (2001):507–532.

[2] Gibaldi M, Perrier D., Pharmacokinetics, 2nd ed. New York: Marcel Dekker.

[3] G. Levy. Pharmacologic target-mediated drug disposition. *Clin. Pharmacol. Ther.* 56:248Y252 (1994).

[4] I. Y. Gong et all. Clinical and Genetic Determinants of Warfarin Pharmacokinetic and Pharmacodynamic during Treatment Initiation. *Plos one*. Vol. 6. e27808 (2011).

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