

MATHEMATICAL AND PHENOMENOLOGICAL CRITERIA IN SELECTION OF PHARMACOKINETIC MODEL FOR M1 METABOLITE OF PENTOXYPHYLLINE

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Abstract

Compartmental analysis transformed „phenomenological models” based on physicochemical and physiological considerations and parameters in „best fitting” models which are essentially empirical. In these conditions all the criteria for selection of best fitting as well as criteria for decision concerning the most significant and with highest prediction power are mainly informative, the final decision having to be validated by phenomenological physico-chemical-physiological considerations.

Pharmacokinetics of pentoxiphylline and its major active metabolites was studied in a bioequivalence study on 24 healthy volunteers. Paper presents the results of mathematical and phenomenological analysis of case of the major active metabolite “M1”. Schwarz, Akaike, Imbibo and Fisher test indicated monocompartmental model as more adequate than bi and three compartmental model. Since metabolite appears in plasma after absorption of pentoxiphylline and distribution in lipid compartment has to be significant following its physicochemical properties, the actual model include at least three compartments. The explanation for this contradiction was considered to be a consequence of large differences between transfer constants, as a degeneration following large differences between transfer and metabolic parameters.

Rezumat

Analiza compartimentală a transformat modelele fiziologice bazate pe parametri și considerente fizicochimice și fiziologice în modele care se potrivesc cât mai bine cu datele experimentale, în fapt modele mai degrabă empirice. În aceste condiții toate criteriile de “cea mai bună fitare” și cea mai bună predicție devin în primul rând informative și trebuie validate de considerații fizico-chimice și fiziologice. Farmacocinetica pentoxifilinei și a metaboliților săi activi majori a fost determinate în cadrul unui studiu de bioechivalență pe 24 de voluntari sănătoși. Lucrarea prezintă rezultatele analizelor matematice și fenomenologice în cazul metabolitului M1. Testele Akaike, Schwarz, Imbibo și F au indicat modelul monocompartimental ca fiind mai adecvat decât modelele bi și tricompartimental. Dat fiind că metabolitul apare în plasmă după absorbția și metabolizarea pentoxifilinei și că, pornind de la proprietățile sale fizico-chimice ele se distribuie semnificativ în compartimentul lipidic, modelul real trebuie să includă cel puțin trei compartimente. Explicația pentru această contradicție a fost considerată ca fiind o urmare a diferențelor mari între constantele de transfer și metabolizare, ducând la un model degenerat în primul rând datorită diferențelor mari între parametrii de transfer și cei de metabolizare.

Keywords: compartmental analysis; pentoxifylline metabolites; optimum model

Introduction

In the general case of n-compartmental models as was conceived by the father of pharmacokinetics Torsten Teorell [1,2], the equations describing the evolution of the concentrations in compartments are

$$\frac{dC_i}{dt} = \sum_{j \neq i}^{1...n} h_{ij} (C_j - C_i), \quad i = 1, 2, \dots, n, \quad (1)$$

where $\frac{dC_i}{dt}$ is the evolution of concentration in time, C_j , C_i – concentrations in compartments and h_{ij} constants.

Since in compartmental theory the concentrations in compartments are independent on space, the term $C_j - C_i$ represents the concentration gradient at the interface between compartments and equation 1 is a special case of Fick first law.

Since mathematically is impossible to find the solution of the above equations best fitting the experimental data, the problem was changed by introduction of new parameters k_i

$$\frac{dC_i}{dt} = \sum_{j \neq i}^{1...n} k_{ij} C_j - k_i C_i \quad (2)$$

where k_{ij} and k_i are all considered independent constants.

This simplification transformed a „phenomenological model” based on physicochemical and physiological considerations and parameters in a „best fitting” model which is essentially empirical [3]. In these conditions all the criteria for the selection of best fitting as well as criteria for decision concerning the most significant and with highest prediction power are mainly informative, the final decision having to be validated by phenomenological physico-chemical-physiological considerations.

Present paper concerns the results of mathematical and phenomenological analysis of case of drugs with active metabolites in high concentrations for which previously the authors had found [4,5,6] contradictions between the two types of analysis methods.

THEORY. STATISTICAL AND INFORMATION CRITERIA IN COMPARISON OF MODELS

Akaike criterion and Schwarz criterion

The Akaike information Criteria (AIC) [7,8,9] and the Schwarz criterion (SC) [10] are somewhat different but each can be viewed as the

sum of the measure of the model-fitting criterion corrected by a “penalty” function proportional to the number of parameters (p) in the model. In least-square analysis with uncorrelated Gaussian errors, the criteria are:

$$AIC = N \ln SS + 2p \quad (3)$$

$$SC = N \ln SS + p \ln N \quad (4)$$

in which SS is the sum of deviations squared with the p -th set of parameters, defined as:

$$SS = \sum_{i=1}^n (c_i^{\text{exp}} - c_i^{\text{calc}})^2 \quad (5)$$

in which C_i^{exp} are the experimental values (in our case plasma levels of concentration) and C_i^{calc} are the concentrations calculated according to the pharmacokinetic model.

The model equation with the smallest AIC and/or Sc is considered to be the “best” representation of the time course plots [11].

Imbibo Criterion [12]

The “mean of confidence limits” of $\hat{c}_i = c_i^{\text{calc}}$ as function of time, $\bar{a}$, is a good estimate of the area between confidence limits (figure 1), and may be defined as follows:

$$\bar{a} = t_{(N-p, 0.05)}^S \quad (6)$$

Then, it may be defined as approximately as:

$$\bar{a} = t_{(N-p, 0.05)} \left[SS \frac{p}{N(N-p)} \right]^{1/2} = t_{(N-p, 0.05)} \left[SS \left(\frac{1}{(N-p)} - \frac{1}{N} \right) \right]^{1/2} \quad (7)$$

The standardized value for this quantity defines the index I_p , for selection of the model:

$$I_p = \frac{t_{(N-p, 0.05)}}{\bar{c}_i^{\text{calc}}} \left[SS \left(\frac{1}{(N-p)} - \frac{1}{N} \right) \right]^{1/2} \quad (8)$$

in which $\bar{c}_i^{\text{calc}}$ is the mean of estimated concentrations versus time. The model equation with the minimum I_p value generates the most restricted confidence limits for estimated released quantities of active substance from the drug.

Analysis of residuals [13, 14]

Analysis of residuals includes first of all examination of distribution of residuals $y_i^{\text{calc}} - y_i^{\text{obs}}$ with naked eye.

In cases of good fitting distribution will be a random one. Systematic deviations of calculated values from the experimental values indicate that there is not a normal distribution and the model is not appropriate.

It is to underline that all these tests do not represent a surrogate of phenomenological specialised analysis of the biological systems to which concerns the model but tests are useful in the choice between models of one which describes well enough the time course of data with a minimum of parameters [15]. The principle of “minimal model” which we could also name “parsimony of parameters” have to keep all the time in mind since a model more complex then necessary would lead to instability in estimation of parameters, to large confidence intervals for predicted parameters as well as to its excessive inter-correlation [16].

Fisher - Snedecor Test

Let us consider two models concerning the same set of experimental data. The random variable

$$F = \frac{SS_q - SS_p}{WSS_p} * \frac{df_p}{df_q - df_p} \quad (9)$$

where df represents the number of degrees of freedom for the respective sum of squares. Here it is to underline that the test makes sense when the two models are „nested” i.e. one model is obtained by „degeneration” from the other by keeping constant some of the parameters.

Experimental methods

Clinical method

Pentoxifylline tablets were administered to healthy volunteers in a cross-over two-period, two sequences bioequivalence study. The study was approved by National Ethics Committee and National Medicines Agency.

Analytical method

Plasma levels of pentoxifylline and its M1 (1-(5'-hidroxyhexyl)-3,7-dimethylxantine) and M5 (1-(3'-carboxypropyl)-3,7-dimethylxantine) metabolites were determined using a Liquid Chromatography/Mass Spectrometry/Mass Spectrometry (LC/MS/MS) validated method.

Computerized methods for estimation of parameters

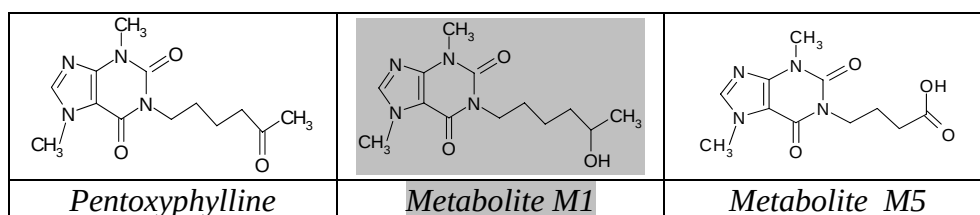
Estimation of parameters was performed using the subroutines of the software TOPFIT 2.0 [17].

In fact, the minimization algorithm used by all software programs in the last 50 years is the Levenberg–Marquardt algorithm [18, 19] that provides a numerical solution to the problem of minimizing a function,

generally nonlinear, over a space of parameters of the function. These minimization problems arise especially in least squares curve fitting and nonlinear programming. The LMA interpolates between the Gauss-Newton algorithm and the method of gradient descent.

Results and discussion

After oral administration, pentoxifylline (3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purin-2,6-dione) is rapidly absorbed and intensively metabolised at the first hepatic passage in two major, active metabolites: 1-(5'-hidroxyhexyl)-3,7-dimethylxantine (M1) and 1-(3'-carboxypropyl)-3,7-dimethylxantine (M5).



We can observe that metabolism transforms the active substance in more polar metabolites: an alcohol and an organic acid.

In spite of a large inter and intravariability of the plasma profiles of the parent drug, the metabolite M1 proved to be more stable and, as can be seen from fig. 1, the mean plasma levels were smooth enough curves not only at steady-state but also after first dose.

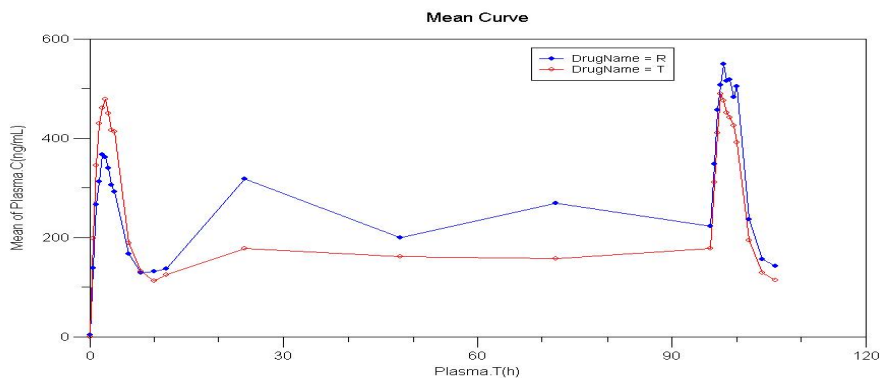


Figure 1

Mean plasma levels of metabolite M1 after single and multiple administrations

Irregular evolution between first administration and last day is a consequence of the fact that, in accordance to the protocol and usual rules of

bioequivalence studies, in the respective period the volunteers were no more hospitalized and food intake was no more standard.

Since „mean data” in the prediction are rather false friends, the modelling selected in the present paper concerns the first volunteer but the results of the much more large set of data led practically to same conclusions.

ONE COMPARTMENT MODEL

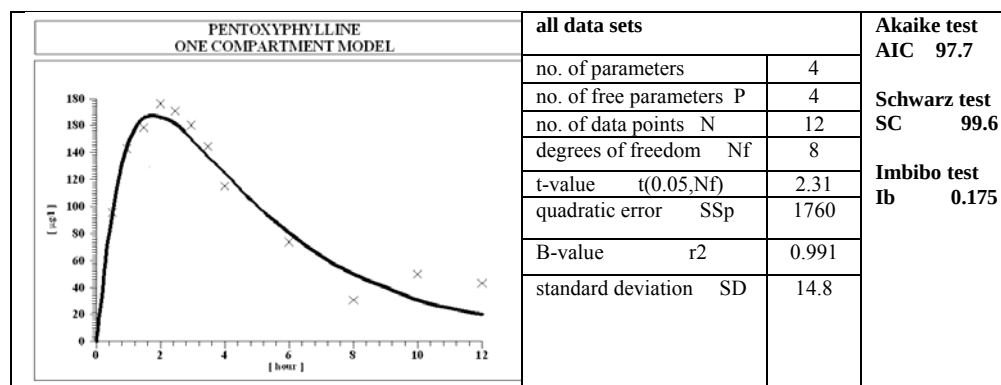


Figure 2

Experimental data, theoretical curve and statistical tests concerning fitting performance

Statistical Tests on Model

Table I

Computed pharmacokinetic parameters starting from monocompartmental model

system parameters, micro constants and coefficients											
flip flop solution no. 1						flip flop solution no. 2					
name	value	t50%	coeff. Zi	AUC	coeff. Ai	name	value	t50%	coeff. Zi	AUC	coeff. Ai
	[1/h]	[h]	[-]	[%]	[-]		[1/h]	[h]	[-]	[%]	[-]
b1	0.224	3.09	1.00	100	1.24	b1	1.15	0.602	1.00	100	-0.242
k1e	0.224					k1e	1.15				
k01	1.15	0.602			-1.24	k01	0.224	3.09			0.242
lag-time parameters						lag-time parameters t _{lag_1} 0.0782 [h]					

Practically the solutions of all compartmental models can be written as linear combinations of exponentials:

$$c(t) = \sum A_i e^{-\alpha_i t} \quad (10)$$

where α_i are the eigenvalues and A_i components of eigenvectors.

As it was discussed above, determination of (A_i, α_i) parameters taking into account the relations between its fitting experimental data is an unsoluble non-linear mathematical problem of minimum with restrictions. In

these conditions the single possibility remains to look for „empirical” solutions (A_i, α_i) free of restrictions.

In the case of monocompartmental models with extravascular administration the situation is somewhat more simple since we obtain a pair of solutions (α_1, α_2) which correspond to phenomenological k_a -absorption constant and k_e - elimination constant but we don't know from mathematical considerations if

$$\alpha_1 = k_a \text{ and } \alpha_2 = k_e \text{ or } \alpha_1 = k_e \text{ and } \alpha_2 = k_a. \quad (11)$$

This is the explanation for the fact that „good” softwares give two „flip-flop solutions”.

In the case of pentoxifylline we have no polar substituents on the molecule and we have to think of it as a more lipophilic than a hydrophilic molecule.

Also since one of the reasons of metabolism is to transform lipophilic compounds in more hydrophilic ones and pentoxifylline has at least two metabolites in significant concentrations – we have another reason to consider pentoxifylline rather lipophilic. Finally since lipophilic substances have good absorption and low elimination in their case $k_a > k_e$.

In the results of TOPFIT k_{le} corresponds to k_e and k_{01} corresponds to k_a . Consequently the correct solution if the model is really monocompartmental, is the flip-flop solution 1.

TWO COMPARTMENTS MODEL

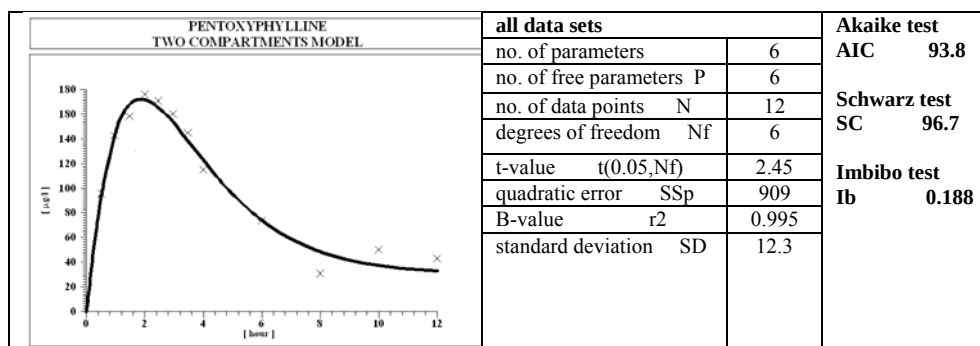


Figure 3

Experimental data, theoretical curve and statistical tests concerning fitting performance

Table II

System parameters, micro constants and coefficients starting from bicompartimental model

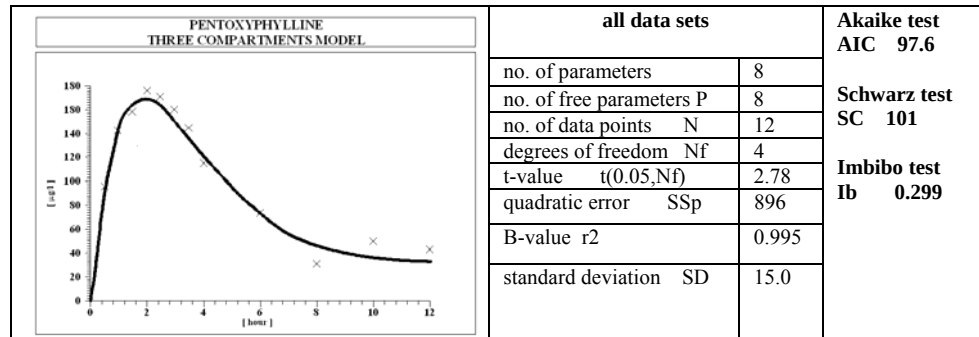
flip flop solution no. 1						flip flop solution no. 2					
name	value	t50%	coeff. Zi	AUC	coeff. Ai	name	value	t50%	coeff. Zi	AUC	coeff. Ai
	[1/h]	[h]	[-]	[%]	[-]		[1/h]	[h]	[-]	[%]	[-]
b1	0.596	1.16	0.918	11.7	104	b1	0.00701	98.9	0.0809	88.3	0.0819
b2	0.00701	98.9	0.0817	88.3	0.0826	b2	0.601	1.15	0.919	11.7	-103
k31	0.0551					k31	0.0551				
k1e	0.0758					k1e	0.0765				
k13	0.472					k13	0.477				
k01	0.601	1.15			-104	k01	0.596	1.16			103
lag-time parameters t _{lag} 1 .0590 [h]						lag-time parameters t _{lag} 1 0.0590 [h]					

Similar to the monocompartmental model we have two „flip- flop,, solutions concerning the identification of transfer constants (k_{13}, k_{31}) between central compartment and second compartment which we consider to be the lipid compartment.

Since we considered above pentoxiphylline more lipophilic than hydrophilic it is normal now to consider that the higher value corresponds to the transfer toward the lipid compartment and the lower one to the back transfer. Consequently we will consider that the flip – flop solution 2 is the correct one.

We also note that the sum of squares of errors in the case of two compartment model is much lower than the sum in the case of monocompartmental modelling.

THREE COMPARTMENTS MODEL

**Figure 4**

Experimental data, theoretical curve and statistical tests concerning performance of fitting starting from three compartmental model

Table III
System parameters, micro constants and coefficients
starting from three compartmental model

flip flop solution no. 1						flip flop solution no. 2					
name	value	t50%	coeff. Zi	AUC	coeff. Ai	name	value	t50%	coeff. Zi	AUC	coeff. Ai
	[1/h]	[h]	[-]	[%]	[-]		[1/h]	[h]	[-]	[%]	[-]
b1	15.0	0.0463	0.533	0.1	-0.0223	b1	0.0010	693	0.0371	98.0	0.0372
b2	0.590	1.17	0.429	1.9	22.8	b2	0.602	1.15	0.430	1.9	-22.4
b3	0.0010	693	0.0379	98.0	0.0379	b3	15.0	0.0463	0.533	0.1	-0.0219
k31	7.28					k31	7.28				
k41	0.0468					k41	0.0468				
k1e	0.0259					k1e	0.0264				
k13	7.11					k13	7.10				
k14	1.10					k14	1.12				
k01	0.602	1.15			-22.8	k01	0.590	1.17			22.4
lag-time parameters t _{lag} 1 0.137 [h]						lag-time parameters t _{lag} 1 0.137 [h]					

Statistical and informatic comparison of models

The results of the informatic tests and statistical F test are summarized in table IV. First of all it is easier to reject the three-compartmental model in favor of the bicompartamental one since all informatic tests have smaller values for bicompartamental model. The value of T-test indicates that by far the lower sum of squares for bicompartamental model (896 face to 909) is a random result.

It concerns the comparison between one compartmental and bicompartamental model the problem is no more so simple as in the previous comparison. Akaike and Schwarz tests voted for bicompartamental model, Imbibo indicates monocompartmental model as better. Further, the F –test indicates that the improvement obtained in fitting experimental data (a decrease of the sum of squares of errors from 1720 to 909) could be a consequence of the increase of the number of parameters but we cannot accept with a 0.90 confidence that the bicompartamental model is more adequate.

Table IV
Comparison of statistical tests concerning performance of fitting of different models

Model	Akaike Test	Schwarz Test	Imbibo Test	F Test	$f_{n,m;0.90}$
Monocompartmental	97.7	99.6	0.175		
Bicompartamental	93.8	96.7	0.188	2.38	4.32
Tricompartmantal	97.6	101	0.299	0.03	

But from the phenomenological point of view we have to think to the distribution of metabolite also in the lipid compartment. Also we have to take into consideration that the source of M1 metabolite is pentoxiphylline, which is

administered orally and has to be released and absorbed before being metabolised. The actual minimal pharmacokinetic model looks like in figure 5.

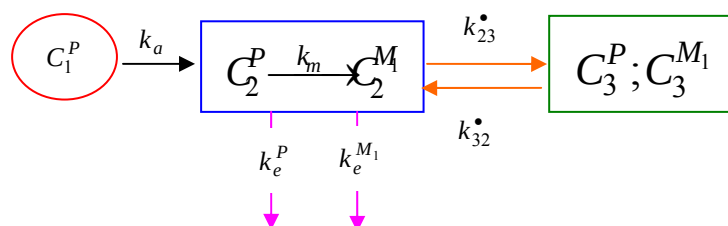


Figure 5

Complete pharmacokinetic model of pentoxifylline and its metabolite M1

Since pentoxifylline is more lipophilic than hydrophilic, since M1 metabolite is more polar than pentoxifylline, it is faithful to suppose the following hierarchy of the transfer coefficients

$$k_a > k_e^P; \quad k_e^{M1} > k_e^P; \quad k_{23}^{M1} > k_{32}^{M1}; \quad k_m > k_e^P$$

Neglecting the smaller constants, the model simplifies to

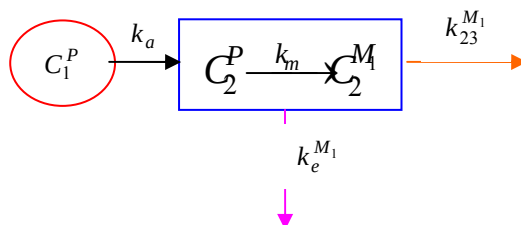


Figure 6

Simplified pharmacokinetic model for pentoxifylline and M1 metabolite

Summing some transfer processes we obtain some “apparent” constants

$$k_e^{M1} + k_{23}^{M1} = k_e^{app}; \quad k_a + k_m = k_e^{app}$$

And the model simplifies once again appearing as a “pseudomonocompartmental” model.

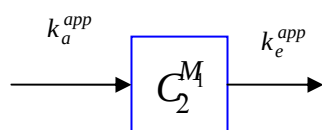


Figure 7

Apparent monocompartmental model for M1 pharmacokinetic

Conclusions

As a general rule, solutions of models present some uncertainties concerning the distribution of eigenvalues between the transfer coefficients, but these uncertainties could be removed starting from physico-chemical properties of the active substance, mainly the partition coefficients between polar and apolar media.

In the case of pentoxifylline we accepted that $k_a > k_e$.

In what concerns the application of mathematical criteria in the selection of the best model for pentoxifylline, it were obtained the following results:

1. Information theory criteria made an hierarchy among models. In our case Akaike, Schwartz and Imbibo indicated as best model the bicompartamental one.
2. Statistical criterion F was used to check the hypothesis that the established hierarchy is a random result or represents a real difference between models. It was found that monocompartamental model has to be preferred.
3. Phenomenological criteria impose as minimal a 4-compartmental model, in order to take into consideration distribution, elimination and metabolism.
4. Contradiction between physico-chemical-physiological considerations and mathematical findings could be explained as a degeneration following large differences between transfer and metabolic parameters.

It is to underline that all these tests do not represent a surrogate of phenomenological specialised analysis of the biological systems which concerns the model but tests are useful in the choice among models of one which describe well enough the time course of data with a minimum of parameters [15].

The principle of “minimal model” which we could also named “parsimony of parameters” has to be kept all the time in mind since a model more complex then necessary would lead to instability in estimation of parameters, to large confidence intervals for predicted parameters as well as to its excessive inter-correlation [16].

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