European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 03, 2020

# Pharmacokinetic Studies Of "Fensulkal" Suppositories And Mathematical Modeling Of Their Parameters.

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***Abstract***

***In recent years, research on the pharmacokinetics of medicinal substances has become of exceptional importance both in terms of increasing the efficiency and safety of drug treatment of various diseases. In the development of a drug, the determining factor becomes the need to ensure a uniform release of the drug from the form-forming component, which is established in in vitro and in vivo experiments. Pharmacokinetic studies of the non-steroidal anti-inflammatory drug phenylglyoxylic acid derivative fensulcal in rectal dosage form suppositories have been studied. The studies were carried out according to the developed methods for the detection and release of fensulcal in biological fluid. According to the dynamics of release in in vivo experiments , it was found that the maximum concentration of fensulcal in the blood was reached after 1 hour. The study of the parameters in the in vitro and in vivo experiments led to the need to calculate the degree of their correlation. A high degree of correlation was established. The results on the value of the correlation coefficient indicating the existence of a direct relationship between the intensity of release in experiments in vitro and its entry into the blood in vivo after rectal administration of suppositories to animals.***

***To assess the effect of a drug and its routes of administration on the rate of absorption of drugs and bioavailability, formalization of their pharmacokinetics was carried out in the form of a one- or two- part model . To assess the pharmacokinetics of Fensulkal suppositories, model-independent parameters were calculated taking into account a 2-chamber model. The results indicate that the maximum amount of fensulcal in the blood is observed 1 hour after administration (P <0.05 ). After reaching the maximum concentration, fensulcal is distributed in organs and tissues at a speed of 504.03 / min. Elimination of the drug proceeded at a lower rate, $K_{\beta}$, $h^{-1}$ = 0.0182. The constants of the fensulcal transition from the central to the peripheral chamber and vice versa are calculated. From the presented data follows $K_{21} >> K_{12}$, which indicates the absence of drug accumulation in the tissues.***

***Key words: pharmacokinetics, fensulcal, mathematical model, bioavailability, suppositories.***

## 1. INTRODUCTION

Bio- pharmaceutical characteristics of any medical supplies (MS) are the basis for detecting drug interactions and the body in order to optimize the treatment regimen. In addition, they are mandatory data for recommending MS for medical use (1,2) .

In recent years, research on the pharmacokinetics of medicinal substances has become of exceptional importance both in terms of increasing the effectiveness and safety of drug treatment of various diseases. It is known that the optimal effect of a drug substance can be ensured by maintaining its concentration in the blood within the therapeutic range. The study of pharmacokinetics, in principle, makes it possible to determine the dosage regimen of the drug, ensuring its rapid creation and long-term maintenance of the average therapeutic level of the drug in the blood and thereby guaranteeing the maximum effect with the minimum risk of side effects. At the same time, when creating new MS, it is necessary to study the bioavailability of the drug - the fraction of the dose and systemic absorption. When developing MS, the decisive factor is the need to ensure a uniform release of the drug from the form-forming component, which is established in in vitro and in vivo experiments (3).

It should be noted that the results of in vitro and in vivo studies should be systematized, i.e. it is necessary to correlate the methods , as well as to study the pharmacokinetic parameters (total clearance, apparent volume of distribution of medicinal substances , average retention time, etc.). The results obtained , depending on the concentration of the medicinal substance and on time, are displayed graphically in a semi-logarithmic coordinate system, which contributes to linearisation curves of kinetics and exercise of schaet calculation parameters . By the nature of the graphic image, the structure of the pharmacokinetics model is established and its parameters are calculated using well-known methods and formulas . ( 4.5 )

**The purpose of the study .** Carry out pharmacokinetic studies of the non-steroidal anti-inflammatory drug phenylglyoxylic acid derivative fensulcal in rectal dosage form in suppositories , formalize them in the form of a one or two-part model and express them in mathematical terms, i.e. to simulate pharmacinetic parameters mathematically .

Pharmacokinetic studies of fensulcal suppositories were carried out according to previously developed methods for the detection and isolation of fensulcal in biological fluid. (6 )

## 2. MATERIALS AND METHODS

The experiments were carried out on outbred male rabbits weighing 1.8-2.2 kg. Throughout the experiment, the rabbits were kept on the usual diet of the vivarium in a standard light mode. The animals were deprived of food one day before the start of the experiment, leaving access to water.

Suppositories were injected into the rectum of experimental animals at a dose of 1.4 mg / kg. Before the introduction of the suppository, the intestines of rabbits were freed from fecal matter by means of a cleansing enema. Blood samples were taken after decapitation of the animals at 0.5, 1, 2, 4, 6 and 8 hours after the administration of suppositories.

The isolated biological materials were subjected to extraction. After a lapse of time, the contents in the tube were acidified and centrifuged. Blood plasma was poured into a separatory funnel, an organic solvent, chloroform, was added and vigorously shaken for 10 min. The extraction was carried out three times. The extracts were subjected to separation in a 0.8 x 6.0 cm column packed with a sorbent - $Al_2O_3$. The last eluate was evaporated to dryness. The dry residue was dissolved in ethanol. The resulting alcohol solution was chromatographed in thin layers of a sorbent under the conditions indicated (7) . In parallel, a

standard solution of fensulcal at a concentration of 0.005% was prepared and subjected to chromatography.

The calculation of the content of the investigated substances in the blood serum was carried out by recalculating the ratio of the total amount of blood to the body weight of the animal. It is known that the ratio of blood to body weight in rabbits averages 5.4%. Based on this, the calculation was made according to the formula:

$$X = \frac{G \times C \times 0.054}{a},$$

where: X is the content of the test substance,%; a - the volume of blood taken for research, ml; G - content of the test substance in the blood volume taken for research, mg; C - body weight of the animal, g; 0.054 is the ratio of the ratio of blood volume to body weight of rabbits.

The experimental results are shown in Fig. 1 and table 1 .

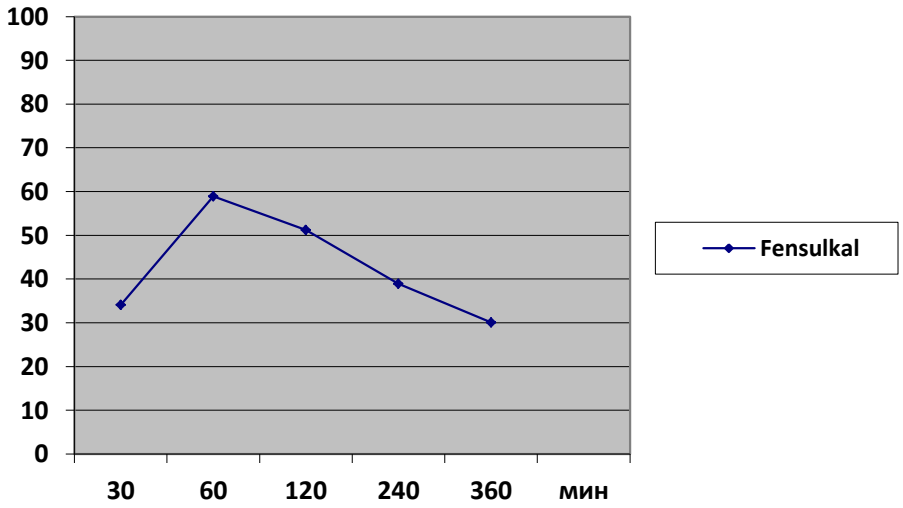


Fig 1 . The dynamics of the release of fensulcal in experiments in vivo

**Table No. 1**
**Fensulcal concentration in rabbit blood**

| Sampling time, min | Found amount, mg | Found amount , % |
|---|---|---|
| 30 | 0.954 | 34.1 |
| 60 | 1,649 | 58.9 |
| 120 | 1,433 | 51.2 |
| 240 | 1.089 | 38.9 |
| 360 | 0.842 | 30.1 |

From the results shown in Table 1 , it follows that the maximum concentration of fensulcal in the blood is reached after 1 hour (58.9 % ).

Studies on the study of pharmacokinetic parameters in in vitro and in vivo experiments have led to the need to calculate the degree of their correlation. We have established a high degree of correlation between the results of the release of fensulcal in in vitro and in vivo (serum) experiments . The quantitative relationship between the results was established through the correlation coefficient ( r ). The results of the correlation analysis are presented in Table 2 .

**Table No. 2**
**Correlation analysis of the results of a biopharmaceutical study of suppositories " Fensulkal "**

| | **30** | **60** | **120** | **240** | **360** | | **X cf; Y cf.** |
|---|---|---|---|---|---|---|---|
| in vitro | 48.3 | 92.3 | 65.1 | 42.9 | 30.1 | | |
| **in vivo** | 34.1 | 58.9 | 51.2 | 38.9 | 30.1 | | |
| **sum (Xi - Xcp)*(Xi - Xcp)*(Yi - Ycp)*(Yi - Ycp)** | **1,097,897.66** | | | | | | |
| **ROOT sum (Xi - Xcp)*(Xi - Xcp)*(Yi - Ycp)*(Yi - Ycp)** | **20169.22351** | | | | | | |
| **CORRELATION r = Sum (Xi - Xcp) * (Yi - Ycp) / ROOT sum (Xi - Xcp)*(Xi - Xcp)*(Yi - Ycp)*(Yi - Ycp)** | **0.885485** | | | | | | |

As follows from the above results, the value of the correlation coefficient indicates the existence of a direct relationship between the intensity of fensulcal release in in vitro experiments and its entry into the blood in vivo after rectal administration of suppositories to animals.

Further, a study was carried out to determine and compose a mathematical model of the pharmacokinetic parameters of the suppositories "Fensulkal" .

The mathematical description of absorption, distribution, elimination and other biological processes that characterize the passage of drugs through a macroorganism greatly contributes to predicting the effectiveness of pharmacotherapy. To assess the effect of the drug and the routes of its administration on the absorption rate of a number of drugs and bioavailability, formalization of their pharmacokinetics was carried out in the form of a one- or two-part model. The parameters of the biexponential equations representing the basic mathematical expressions of these models are determined by the sequential logarithm and least squares methods, which are calculated using specially created programs or well-known techniques and formulas (8, 9) .

To assess the pharmacokinetics of Fensulkal suppositories, model-independent parameters were calculated taking into account a 2-chamber model: maximum concentration ($C_{max}$), time to reach it ($T_{max}$), half-life ($T_{1/2}$), area under the pharmacokinetic curve ( AUC ), clearance ( Cl ), volume of distribution ( V ) and mean retention time ( MRT ).

Mathematical modeling of the results of determining the pharmacokinetic parameters of suppositories "Fensulkal" in the blood serum of rabbits are presented in Table 3 .

**Table No. 3**
**Pharmacokinetic parameters of fensulcal in rabbit blood serum**

| **No.** | **Defined parameter** | **Fensulkal** |
|---|---|---|
| 1 | Half-absorption period $T_{0.5}$, min | 7 8,170 |
| 2 | Half-life $T_{0.5}$, min | 5 0 4.03 |
| 3 | Maximum concentration in serum at $T_{max}$, mg / ml | 1.69 |
| 4 | Elimination rate constant $K_{\beta}$, $h^{-1}$ | 0.01 82 |
| 5 | Half-life $T_{0.5}$, min | 1 46.4 |

| | | |
|---|---|---|
| 6 | Total volume of distribution V , ml | 0.151 |
| 7 | Total clearance CI | 0.003 |
| 8 | Area under the concentration-time curve, $AUC_{\infty}$ | 1 8763 28.5 |
| 9 | Time to reach the maximum concentration of the drug in the blood, h | 1 |
| 10 | Average retention time, MRT , h | 20 1.1 |
| 11 | Transition rate constant: from the peripheral chamber to the center. $K_{21}$ , $h^{-1}$ | 0.0132 |
| 12 | Transition rate constant: from center. cameras in the peripheral $K_{12}$ , $h^{-1}$ | 0.00 5 |

From the results obtained, it follows that the maximum amount of fensulcal in the blood is observed 1 hour after administration ($P < 0.05$). After reaching the maximum concentration, fensulcal is distributed in organs and tissues at a rate of 504.03 / min. Elimination of the drug proceeds at a lower rate, $K_{\beta,}$ $h^{-1} = 0.0182$.

To assess the possible toxic effect of suppositories, the constants of fensulcal transfer from the central chamber to the peripheral chamber and vice versa were calculated. As follows from the presented data $K_{21} >> K_{12}$, which indicates the absence of drug accumulation in the tissues.

## 3. RESULTS AND DISCUSSION

Pharmacokinetic studies of a non-steroidal anti-inflammatory drug, phenylglyoxylic acid derivative fensulcal in rectal medicinal form, suppositories have been studied . The studies were carried out according to the developed methods for the detection and isolation of fensulcal in a biological fluid. According to the dynamics of release in experiments in vivo , it was found that the maximum concentration of fensulcal in the blood is reached after 1 hour. Studies of the parameters in in vitro and in vivo experiments led to the need to calculate the degree of their correlation. A high degree of correlation was established. The results on the value of the correlation coefficient, which indicated the existence of a direct relationship between the intensity of release in experiments in vitro and its entry into the blood in vivo after rectal administration of suppositories to animals.

To assess the effect of a drug and its routes of administration on the rate of absorption of drugs and bioavailability, formalization of their pharmacokinetics was carried out in the form of a one- or two-part model. To evaluate the pharmacokinetics of suppositories "Fensulkal" model-independent parameters are calculated with the two-chamber modeli. Obtained results showed , that the maximum number fensulkal blood observed after 1 hour after ingestion ($P <0.05$ ). After maximum concentration fensulkal distributed in organs and tissues at a rate of 504.03 / min. Elimination of the drug proceeded at a lower rate, $K_{\beta}$ , $h^{-1} = 0.0182$. The constants of the fensulcal transition from the central to the peripheral chamber and vice versa are calculated. From the presented data follows $K_{21} >> K_{12}$, which indicates the absence of drug accumulation in the tissues.

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