The Comparative Evaluation of The Renal Clearance for two Products Based on Pyrantel, on a Group of Cats Used in a Bioequivalence Study

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Abstract

The clearance is a pharmacokinetic measurement of the renal excretion representing the plasma volume completely cleared by the substance, in a certain amount of time (Rowland and Tozer, 2011); it is usually measured in l/h for drugs. The total clearance of the body represents the sum of the metabolic clearance and the renal clearance (Hauschke *et al.*, 2007). As the half time ($t_{1/2}$) shortens, the drug will be eliminated faster and the absorption period will be shorter (Cristina and Chirciu, 2010).

The purpose of this study was to evaluate the renal clearance of two products based on pyrantel (the tested product and the reference product). The measurements were carried out with regard to the half time and the maximum plasmatic concentration of the drugs.

A number of 12 cats were included in the study; clinically healthy of European breed. According to the testing protocol, the cats were administered pyrantel in a concentration of 230 mg, in two stages, following a randomized list. Before and after administration, 11 blood samples were collected, at different intervals of time, for three consecutive days. The main parameters determined were: renal clearance, half-time of the drug and the maximum concentration in blood.

It was observed, that for the same concentration of pyrantel pamoate (230 mg), the clearance was different for the two groups: for the first group, the clearance was 0.84 ± 0.44 mg/h, respectively 0.58 ± 0.38 mg/h for the second group. The half time was 1.58 ± 0.68 hours for the first group while for the second group, it was 2.38 ± 1.05 hours. These values were recorded when the maximum concentration was recorded (1.5 ± 0.85 hours for group 1 and 2.29 ± 2.09 hours for group two). The comparative analysis of the levels from the analyzed data revealed differences given mainly by individual fluctuations, which were situated within the bioequivalence standards.

Keywords: *bioequivalence, clearance, half-life, pyrantel pamoate*

INTRODUCTION

Bioavailability represents the percentage of a administered pharmacological product that enters the blood stream, after administration. For the same active substance, its bioavailability may vary according to the species and subject. The oral bioavailability it is influenced by the size, lipophilic character, the electrical charge and the bonding to food particles of every tablet (Criveanu, 2008; Cristina and Chirciu, 2010).

The maximum concentration (C_{max}) displays the maximum value reached in the blood, after administering the drug (Tracy, 2004). C_{max} also shows the rate and extent of absorption, linked especially with the clearance of the subjects' body. For example, a drug with a poor absorption and a moderate rate of elimination will not accumulate in the body, presenting a weak pharmacodynamic effect.

The half time ($T_{1/2}$) reveals the necessary time for the plasmatic concentration of the drug,

to decrease by 50%. $T_{1/2}$ is important to determine the necessary time for the concentration of the active substance to reach a plateau concentration. At the same time, $T_{1/2}$ reveals the moment when the active substance will be eliminated from the body after administration, allowing the adjustment of the doses in the case that there are necessary multiple dosages (Trepanier, 2013).

The clearance is a name used specifically in pharmacokinetics and it refers to the volume of plasma completely cleaned of the active substance, in an amount of time (Rowland and Tozer, 2011). The clearance reflects all routes of elimination of the drug, including biotransformation, biliary excretion, glomerular filtration and tubular secretion (Hauschke *et al.*, 2007, Ritter *et al.*, 2008). The shorter the half-life of the drug, the more rapidly it will be eliminated from the body and maximum period of absorption will be shorter (Cristina and Chirciu, 2010).

The evaluation of the results obtained in the following study, started from the premise that bioequivalence of two products is achieved when, between the tested product and the reference one are only small differences regarding their systemic bioavailability (Ognean, 2008).

MATERIALS AND METHODS

The research was conducted in the faculty of Veterinary Medicine, Cluj-Napoca, in the Depart-

ment of Physiology, during a period of three months (March – May 2013).

In this study, 12 clinically healthy cats were included, European breed, coming from both rural and urban areas. The animals were selected using rigorous inclusion/exclusion criteria. During the period of the study, the animals were housed and fed according to the protocol. Administering the tablets was done according to a randomization list.

The active substance, pyrantel, was given for both the tested product and the reference in a concentration of 230 mg. This way, it was easier to analyze the pharmacokinetics of its molecules. The bioequivalence testing was performed in two phases, separated by a washout period of 14 days.

Eleven blood samples were collected, for three consecutive days, at different time periods (Tab.1).

The cats' health status was evaluated during the study, according to the protocol from table 2; for this purpose, clinical, hematological and biochemical test were carried out. All the subjects who did not correspond in terms of hematological, biochemical or clinical results were eliminated from the study.

Tab. 1. Exact hours at which the blood samples were collected

Day 1	(0.0) and 0.5, 1.0, 1.5, 2, 4, 8, 12,
Day 2	24.0, 36.0
Day 3	48.0

Tab. 2. The examination protocol

Procedure	Screening	Phase I				Wash-out 7-14 days	Phase II				Final exami- nation
Study day	-7...-1	0	1	2	3		0	1	2	3	+7
Volunteer information and written consent	●										
Verification of inclusion/exclusion criteria	●	1			1						
Physical examination	1										1
Vital signs	1		1					1			1
Clinical chemistry	1										1
Hematology	1										1
Urinalysis	1										1
Serology	1										
Product administration			1					1			
Blood collection for drug concentrations measurement			1	1	1			1	1	1	
Adverse Events observing and recording		1	1		1	1	1				

In order to determine the bioequivalence parameters, the Kinetica 5.0 software was used. For this study, only the following parameters were of interest: Clearance; Peak concentration ($C_{\max}$); Half-life ($T_{1/2}$)

The statistical interpretation of the data obtained was carried using ANOVA by means of the Tukey-Kramer Multiple comparisons test. The statistical analysis was carried out using GraphPad software version 3.05; the charts were generated using the OriginPro 8.5 software.

RESULTS AND DISCUSSION

The chemical analysis of the tested formulas showed that regarding the praziquantel, the active

substance was administered in equal amounts for both the reference and tested product (230 mg).

Regarding the maximum concentration of the active substance, the average results were 116.24 ± 55.15 ng/mL for the tested product and 148.91 ± 96.81 ng/mL for the reference product (Fig. 1).

Also, in the case of the reference drug administered, there was a maximum recorded value of 362.69 ng/mL, compared to the maximum value recorded in the case of the tested product – 210.1 ng/mL.

The mean values obtained for the half-time ($T_{1/2}$) of the two products, were close at range, with a mean of 1.58 ± 0.68 h for the tested product and 2.38 ± 1.05 h for the reference drug (Fig. 2).

Fig 1. Individual variations of $C_{\max}$ for the tested product (group T) and for the reference (group R)

Fig. 2. Fluctuations recorded for the tested drug and for the reference, regarding the half-life of praziquantel

For the tested product there was registered a minimum value of 1.12 h and a maximum value of 3.56 h. Comparatively, the maximum value obtained for the reference product was of 4.42 h.

For the clearance there were higher values obtained in the case of the tested product, with a mean of 0.84 ± 0.44 mg*h/(ng/mL), compared to the reference product, were a mean value of 0.58 ± 0.38 mg*h/(ng/mL) was recorded (fig. 3). For the tested product, a maximum value for the clearance of 1.7 mg*h/(ng/mL) was recorded, compared to 1.28 mg*h/(ng/mL), the maximum value obtained for the reference product.

Pyrantel pamoate is an anthelmintic drug, with a low systemic availability. Its peak serum concentrations occur 1–3 hours after a administration (McEvoy, 2009). It is partially metabolized in the liver and approximately 50% of an oral dose is excreted through feces and only a small portion through the kidneys (Maddison, 2008).

Although the concentration of the active substance was the same for the tested and reference products, the determined parameters showed individual variations, without any statistical significance, the two products being bioequivalent.

C_{max}. Regarding the peak concentration of the active substance, it was observed that there were high fluctuations of the recorded results for the tested product compared to the reference one, although the same amount of pyrantel pamoate was administered for both (fig.1). Thus it can be observed that the active substance, pyrantel, from the reference drug, was absorbed to a larger extent compared to the tested product.

However, analyzing the individual results for the tested product, there were smaller variations compared to the reference product, showing a more stable absorption for the tested product. Small fluctuations were recorded for the individual results, compared to the mean results for both products.

Both the maximum and minimum values recorded for the tested product were higher than the minimum and maximum results recorded for the reference product. Similar studies performed on dogs (Morovján *et al.*, 1998; Ognean *et al.*, 2008), demonstrated that the substance, pyrantel pamoate, has a good absorption in the body.

T_{1/2}. Regarding the half-life (T_{1/2}) of pyrantel pamoate, there were variations between the tested product and the reference, with a higher variability for the reference product (Fig. 2).

Similar to the maximum concentration, also for the half-life of the product, the individual values recorded for the tested product varied non-significant from the mean results.

For the tested product there was recorded a minimum value of 1.12 h and a maximum value of 3.56 h. Comparatively, the maximum value obtained for the reference product was 4.42 h. The half-life of the product along with the clearance, show how well the active substance is being eliminated from the body.

Clearance. The results obtained for the clearance of the pyrantel showed a fluctuating trend both for the reference drug and also for the tested product (Fig. 3).

Fig. 3. Clearance for the tested drug and for the reference

Correlated with the half-life of the substance, it can be observed that the tested product is being eliminated slower from the body, although its half time is faster compared to the half time of the reference product.

A similar study regarding the pharmacodynamics of pyrantel was performed on horses, proving that pyrantel pamoate is eliminated mainly by feces (Gokbulut *et al.*, 2001).

Another study carried out on pigs, compared the pharmacokinetics of oral pyrantel versus the intravenously administered pyrantel. It was observed that the intravenously administered pyrantel it is distributed faster in the body, reaching its peak concentration sooner than the oral product. Nevertheless, its short time of persistence in the organism indicates that the oral product has an increased efficiency on a long-term (Bjorn, 1996).

CONCLUSIONS

Administering an equal quantity of pyrantel, both for the tested product and for the reference drug (230 mg), similar evolutions have been recorded for the investigated parameters (C_{max} , T_{max} and clearance). Analyzing the individual results obtained, it was observed a varying trend both for the tested and reference product.

Regarding the peak concentration, pyrantel was absorbed in a higher quantity in from the reference product, compared to the tested drug. This is a positive aspect due to the fact that there is a greater quantity of active substance available in the bloodstream, not being necessary to supplement the doses.

The half-time of pyrantel was longer for the reference product, compared to the tested product. This aspect, linked to its bigger absorption, makes its anti-parasitic action more efficient.

With regard to the clearance, this was faster for the reference product, thus the residues won't last for long in the body.

The individual results recorded for the tested product had smaller variability regarding pyrantel

pamoate, this way being much more stable in regard to its pharmacokinetics.

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