A bioequivalence study on two closantel oral suspensions in sheep: an Iranian product (fascinil®) versus flukiver® as a reference product

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Abstract:

BACKGROUND: Closantel is a broad-spectrum antiparasitic agent and is widely used for the control of Fasciola spp. and Haemonchus spp. infestations in sheep and cattle. **OBJECTIVES:** The present study was carried out to evaluate the bioequivalence of a domestic closantel formulation, Fascinil® (Damloran Pharmaceutical Co., Iran), in comparison with Flukiver® (Janssen pharmaceutical Co., Belgium) in sheep. **METHODS:** In a parallel design, twenty-eight male sheep, 4- 5 months of age, were randomly divided into two groups. First group received a single dose of Fascinil® oral suspension as a test product at 10 mg/kg BW, and the second group received Flukiver® as a reference product with the same dose. Blood samples were taken on 0, 4, 8, 12, 16, 20, 24, 32, 48, and 72 hours after drug administration, and the plasma concentrations of closantel were determined using a high performance liquid chromatographic (HPLC) method. Pharmacokinetic analysis was performed; in addition, the areas under the plasma concentration-time curves at 0-72h (AUC0-72), maximum plasma concentrations (Cmax), and times to reach Cmax (Tmax) of the closantel in test and reference groups were compared. **RESULTS:** There were no significant differences in the AUC0-72 (2913.00±648.18, 2957.88± 623.41 µg.h/mL), Cmax (62.22±7.74, 71.71±13.03µg /mL), and Tmax (23.38±4.27, 23.23±4.28h) between Fascinil® and Flukiver®, respectively. The 90% confidence intervals for test: reference ratios of these pharmacokinetic (PK) parameters were within bioequivalence acceptable range (80-120%). **CONCLUSIONS:** It is concluded that the test product (Fascinil®) and Flukiver® are bioequivalent, and they can be used as interchangeable anthelmintic drugs.

Introduction

Closantel is a halogenated salicylanilides with a potent antiparasitic activity and is extensively used to control Haemonchus spp. and Fasciolla spp. infestations in sheep and cattle and Oestrus ovis in sheep in many parts of the world (Swan, 1999, Sargison, 2011). It is highly effective for the treatment of adult flukes and it shows good activity against immature flukes aged 6 to 8 weeks. This compound is also effective against a large number of internal parasites, in particular haematophagous helminths, and certain external parasites including blood-sucking lice, ticks, and mites in a variety of animal species (Swan, 1999; Lanusse et al., 2009). This drug is also used in combination with other antihelminthic

agents, such as ivermectin, because of its convenience and potential synergistic action (Sargison, 2011).

The mode of closantel action is believed to be caused by an interference with energy metabolism in the liver fluke by uncoupling oxidative phosphorylation. However, other potential mechanisms may also contribute to the overall drug efficacy (Fairweather and Boray, 1999; Lanusse et al., 2009).

The unique pharmacokinetic characteristics of closantel appear to play an important role in its efficacy and safety (Swan, 1999). Closantel is a weak acid molecule (pKa=4.28) and highly lipophilic. It is formulated as 3.75 or 5% suspensions or solutions for oral drench or intraruminal administration. Closantel solutions may also be used for parenteral (SC or IM) administration. It is well absorbed after enteral or parenteral dosing in sheep and cattle. The recommended enteral dose in sheep is 10 mg/kg; the same efficacy could be attained by SC or IM dosing of 5 mg/kg, indicating that its oral bioavailability seems to be 50% lower compared to that of parenteral administration. Although closantel is not subject to any significant metabolism by ruminal fluid, its absorption following oral dosing in ruminants is incomplete. The low bioavailability may be due to a strong association of closantel with particulate digesta and being mostly in ionized form at the absorption site in the intestine (Hennessy and Ali, 1997; Swan et al, 2000; Lanusse et al., 2009).

Closantel is extensively (>99%) bound to plasma proteins, mainly albumin, and it has a long terminal half-lifes in sheep; about 14 and a half days (Mohammad- Ali and Bogan 1987; Lanusse et al., 2009). Owing to its high protein binding, the duration of therapeutic levels of closantel in plasma is prolonged. Thus, a single dose of closantel protects sheep against susceptible H. contortus reinfection for up to 28 days. On the other hand, it has a small volume of distribution (<0.15 L/kg), with limited distribution of drug to tissues (including liver) in ruminants. Thus plasma albumin constitutes a drug reservoir that is directly available to haematophagous parasites, such as F. hepatica and H. contortus (Michiels, 1987; Swan, 1999; Lanusse et al., 2009). Tissue concentrations of closantel are extremely low in sheep, 7-21 times lower than its plasma concentration, and tissue levels decline in parallel to plasma levels (Lanusse et al., 2009, Sargison, 2011).

It has been shown that the clinical efficacy of anthelmintics is closely related to their pharmacokinetic profiles and that the plasma availability of drug can be affected by the formulation and route of administration (Lanusse and Prichard, 1993; Swan et al, 2000; Garedaghi et al., 2011).

Recently, Eslami et al. (2006) carried out a study on the bioequivalence of an oral suspension of albendazol produced in Iran, in sheep. The authors found that the domestic (generic) product was not bioequivalent to the reference product (Valbazen®, Pfizer Inc.). Therefore, because of the importance of closantel in prevention and treatment of parasitic disease and the lack of reports for blood-level bioequivalence studies on closantel oral suspensions formulated in Iran, the present study was conducted to evaluate Fascinil® (as a test product) in comparison to Flukiver® (as a reference product) in sheep.

Materials and Methods

Animals: Twenty-eight healthy male lambs (aged 4 to 5 months, 37.75±5.59 kg) were used in the present study. The animals were randomly divided into 2 groups of 14; Fascinil® (Test) and Flukiver® (Reference) groups. They had free access to water and feedstuff ad libitum daily.

The lambs were kept for a week to adapt, and then each animal received a single dose of 10 mg/kg BW of the test product (Damloran Pharmaceutical Co., Iran) or reference product (Janssen Pharmaceutical Co., Belgium). An automatic drench gun was used for drug administration.

Blood sampling: Blood samples (about 6 ml in each case) were collected through jugular vein just before closantel administration (0 h) and 4, 8, 12, 16, 20, 24, 32, 48, and 72 h after the drug administration and were immediately transferred into heparinized tubes. The samples were centrifuged for 10 min at 2500 rpm, and their plasma were collected. The plasma samples were stored at -80 ^{o}C until analysis.

Sample preparation and extraction: Sample preparation and purification were carried out using the method described by Stove, 1998, with some modifications as follows: 1 mL plasma sample transferred to a tube along with 1 mL of a saturated sodium chloride solution containing 0.05% con-

centrated acetic acid. They were mixed, afterwards 10 mL acetonitril was added and then mixed by a vortex mixer for 7 min. The solution sonicated for 10 min in an ultrasonic bath (Power Sonic 505, Hwashin Tech Co., South Korea) and centrifuged for 10 min at 2500 RPM. The supernatant layer was taken and evaporated to a volume of about 1 mL, using a rotary evaporator (Heidolph 2, Germany) at 40^{o}C. Then, the supernatant layer was dried under the flow of nitrogen gas. 2 mL of acetonitrile was added to the tube containing dried sample, and vortex mixed and sonicated for 2 min. The 3 mL cartridges, containing 500 mg C18 (Resprep Co., USA), were used for purification. Cartridges were conditioned by 5 mL acetonitril and 5 mL ethanol. The sample solution eluted through the C18 cartridge using a vacuum pump (Fast Vac, USA) and then washed by 5 mL acetonitril. Both solutions were collected and evaporated and dried as mentioned above. The samples were stored at -20^{o}C until HPLC analysis for closantel concentration.

HPLC analysis of samples: The samples were reconstituted in 1.0 mL acetonitrile and filtered through a 0.45 µm filters (Millipore Co., USA), and 50 µL aliquots of the reconstituted samples were injected into the HPLC system using the HPLC method described by Stove, 1998.

The HPLC system comprised a Wellchrom K1001 multisolvent pump (Knauer, Germany), an Online Degasser (Knauer, Germany), a Dynamic mixing chamber (Knauer, Germany), a Triatlohn auto-sampler (Spark, Netherland), a Wellchrom V7566 Interface Box pump (Knauer, Germany), and a Waters 420 fluorescence detector set at 335 nm as excitation wavelength and 510 nm as emission wavelength for monitoring the signals. The column was an Eurosphere-100 C18, 5µm, 300 x 4.0 mm (Knauer, Germany) and it was used at room temperature. The mobile phase was an acetonitril: buffer (10 mM K2HPO4, pH=2.5) mixture (80:20 v/v) with a flow rate of 1.0 mL/min. The run time was 10 min.

The samples of plasma collected from drug naive animals were spiked with closantel standard (a gift from Janssen Pharmaceutical Co., Belgium) to prepare standard solutions in the range of 0, 10, 20, 40, and 80 µg/mL. Closantel calibration curve was made using peak areas of chromatograms of extracted samples of spiked plasma. The analytical method was validated for specificity (lack of interfering peak), range of detection, and sensitivity, which is defined as limit of detection (LOD), and limit of quantification (LOQ), as well as linearity of the response as R2 of the calibration curve. Recovery was also determined from HPLC assays of different closantel concentrations spiked in plasma samples taken from non-treated animals. Plasma closantel levels of each time point samples for individual animals of test and reference groups were calculated through their corresponding HPLC peak areas using calibration curve formula.

Pharmacokinetic analysis: Closantel concentration-time data in plasma of each animal were submitted to a non- compartmental analysis model. Pharmacokinetic (PK) parameters including AUC, Cmax, and Tmax for individual animals, as well as their means± standard deviation (SD) for reference and test drug groups, were obtained. The linear trapezoidal rule was used to calculate areas under concentration-time curves from 0-72 h (AUC 0-72).

Bioequivalence/Statistical analysis: Comparative bioavailability or bioequivalence were analyzed by comparing the PK data (AUC0-72, Cmax and Tmax) of reference and test groups by independent t test and 90% confidence interval of ratios of the PK values for the two formulations using SPSS software. Data were reported as mean±SD, and the differences were considered significant when $p<0.05$.

Results

Analytical method validation data and calibration curve: The representative chromatograms for the extracted plasma samples, including blank plasma, a plasma spiked with closantel standard solution, and a plasma sample collected from a sheep following oral dosing of a closantel formulation are shown in Figure 1. The chromatograms shown in Figure 1 indicate a good separation for closantel peak (specificity or lack of interfering peak). Retention time for closantel was approximately 7.5 min. Suitable linearity of the closantel calibration curve at drug concentration range of 0-80 µg/mL was obtained as R2=0.9961 (Figure 2). Limit of detection and limit of quantification of the method were 3 and 10 µg/mL, respectively. Recovery rate of the

Table 1. Closantel plasma pharmacokinetic parameters obtained in each animal following a single oral dose of two closantel product, Fascinil® as a test or Flukiver® as a reference drug, at 10 mg/kg in sheep.

Sheep No.	PK parameter					
	AUC 0-72 (µg.h/mL)		C max (µg/mL)		T max (h)	
	Reference	Test	Reference	Test	Reference	Test
1	3614.10	3988.61	82.61	74.33	16.00	20.00
2	3444.28	3234.55	70.97	61.42	24.00	32.00
3	3177.77	3379.08	80.47	73.70	20.00	20.00
4	3513.93	3801.23	81.92	71.46	16.00	32.00
5	4022.37	2241.56	90.14	65.25	24.00	20.00
6	3267.29	2668.02	83.58	51.05	20.00	24.00
7	3109.35	2498.13	84.24	61.67	24.00	24.00
8	3283.70	2522.82	60.04	55.69	28.00	20.00
9	2626.85	3125.63	75.24	60.76	24.00	20.00
10	2457.44	1587.69	58.58	55.24	32.00	24.00
11	2553.38	3245.61	65.33	68.54	24.00	24.00
12	2154.77	2345.11	54.33	51.92	24.00	24.00
13	2133.11	2878.70	69.24	56.08	28.00	20.00
14	2051.94	3265.22	47.25	63.92	24.00	20.00
Mean	2957.88	2913.00	71.71	62.22	23.23	23.38
SD	623.41	648.18	13.03	7.74	4.28	4.27

Table 2. Comparison of bioequivalence indices obtained for closantel following a single oral dose of Fascinil®, as a test and Flukiver® as a reference drug at 10 mg/kg in sheep (n=14 each group).

PK parameter	Reference drug (Mean± SD)	Test drug (Mean± SD)	90% Confidence interval	p Value
AUC(0-72 h), (µg.h/mL)	2957.88±623.41	2913.00±648.18	89-113%	0.83
Cmax, (µg/mL)	71.71±13.03	62.22±7.74	81-98%	0.08
Tmax, (h)	23.23±4.28	23.38±4.27	89-117%	0.93

extraction method was 81.8±16.8.

Pharmacokinetic data: Pharmacokinetic data for two groups of sheep receiving reference and test formulations are shown in table 1. Mean closantel plasma concentration- time profiles of two treatment groups are plotted in Figure 3. The data for comparisons of bioequivalence parameters obtained from reference and test groups are shown in table 2. As can be seen table 2, there were no significant differences between PK parameters of the two treatment groups. Moreover, the 90% confidence intervals for test, reference ratios of the bio-equivalence indices, were within acceptable range (80-120%).

Discussion

Closantel is widely used against a number of parasitic diseases, in particular for the prevention and treatment of blood-feeding helminthes such as Fasciolla hepatica and haemonchus contortus infestation in sheep (Swan, 1999). These parasites greatly limit sheep production and cause suboptimal animal productivity, mostly due to the direct effects of their blood-feeding behavior (Sargison, 2011). This compound is characterized by high plasma protein binding, low tissue residual, little biotrans-formation and long duration for therapeutic action (Lanusse et al., 2009, Sargison, 2011). Several commercial domestic and international pharma-ceutical preparations for closantel oral suspension are currently available. The generic products of closantel seeking approval to enter the market should demonstrate their ability to achieve bioavailability values including AUC and Cmax or bioequivalence to that of the original formulation. When two medicinal products are bioequivalent, their therapeutic function would be the same in target animals. The inability to maintain high enough blood levels for sufficient periods of time may result in a therapeutic failure or substandard therapeutic action.

To determine the bioequivalence of two pharma-ceutical products, regulatory agencies have set a certain criteria. The criteria specify that the mean AUC and Cmax values of the test product should not be more than 20% different from the corresponding mean values of the reference product. This can be expressed as $0.80 < \mu T/\mu R < 1.20$, where µT and µR denote the mean value of PK parameter of interest for the test and reference products, respectively (Toutain

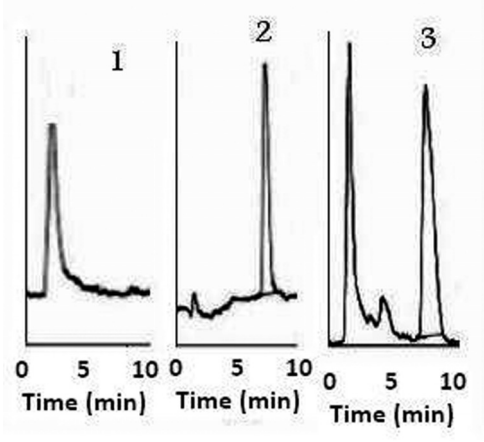

Figure 1. The chromatograms of closantel HPLC analysis following sample extraction: 1. A blank plasma sample, 2. A plasma sample spiked with closantel standard solution, 3. A plasma sample collected from a sheep following a single oral administration of closantel suspension (at 10 mg/kg).

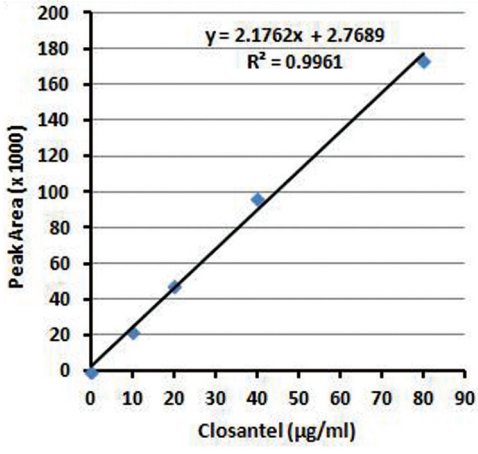

Figure 2. Closantel calibration curve depicted using the chromatogram peak areas of the plasma samples spiked with 0-80 µg/mL of closantel reference standard and analyzed by HPLC system.

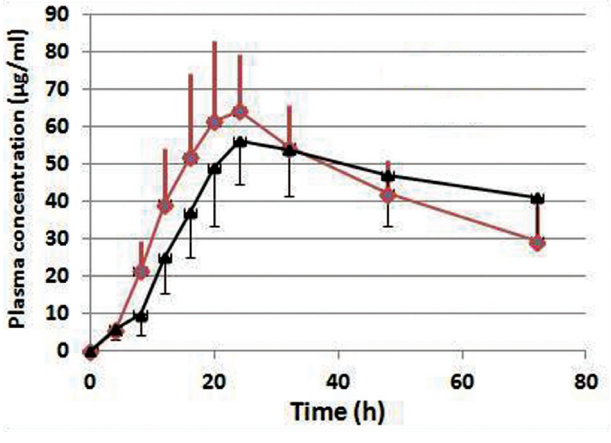

Figure 3. Plasma closantel concentration- time profiles obtained by single oral administrations of two closantel formulations, Fascinil® as a test and Flukiver® as a reference product, at 10 mg/kg in sheep (Mean±SD, n=14 each group).

and Koritz, 1997; FDA, 2006; Eslami et al., 2006).

This project was conducted to evaluate the bioequivalence of two closantel oral suspensions Fascinil® as a test, and Flukiver® as a reference drug in sheep at 10 mg/kg BW, according to the dosage recommended by the manufacturers. Due to a long elimination half-life of closantel in sheep, a parallel design was adopted, and three PK parameters (AUC, Cmax and Tmax) were compared to evaluate the rate and extent of oral absorption of closantel formulations.

The results showed that there were no significant differences between the PK data obtained from the test and reference products. Moreover, the 90% confidence interval for the ratios of AUC0-72, Cmax, and Tmax values between test and reference formulations were within acceptable bioequivalence range (80-120%).

Among PK parameters, AUC is believed to be a more important factor in bioequivalence studies, and it reflects the general exposure of the body to the drug. AUC0-72 value in test group (2913.00±648.18 µg.h/mL) was very close to the AUC0-72 value in the reference group (2957.88±623.41 µg.h/mL), indicating much similar PK profiles and extents of oral absorption.

The plasma availability of drugs can be affected by the formulation and route of administration, and it has been shown that the clinical efficacy of anthelmintics is closely related to their PK profiles (Lanusse and Prichard, 1993; Garedaghi et al., 2011). Clinical endpoint studies for the evaluation of the bioequivalence of the generic closantel formulations are associated with a number of difficulties and may be confounded by so many interfering variables related to host or parasitic agent. However, plasma-level bioequivalence studies are more reliable and straightforward for demonstrating product bioequivalence. In addition, blood level measurements are "closer" to the critical formulation in the dose-response process, from the point of drug administration to ultimate therapeutic effect (Martinez et al., 2002; Garedaghi et al., 2011).

In a similar bioequivalence study using a different

dosage form, Arab et al. (2010) administered a 500 mg closantel bolus per capita in 15 sheep, orally (40-50 kg BW). They reported 2049 ± 421.2 µg.h/mL for AUC 0-72. By comparing the results of the present study with these data, it can be seen that different AUC 0-72 value indicate that the bioavailability of closantel oral suspension is more than that of oral bolus formulation. Therefore, using a different dosage form may implicate in clinical effectiveness of closantel and its duration of action.

In the present study, Cmax value in test group (62.21±7.74 µg/mL) was to some extent lower than that of Cmax value in reference group (71.71± 13.03µg/mL); however, in the acceptable range. These Cmax values for closantel are comparable to and somewhat higher than those reported by Arab et al. (2010), 56.38 ± 14.28; Croubels et al. (2009); 56.5 µg/mL, and Michiels et al. (1987), 48-62 µg/mL.

The Tmax value obtained from the test group (23.38±4.27h) was similar to that of Cmax value in the reference group (23.23±4.28h). These Tmax data for closantel were also comparable to those reported by Arab et al. (2010), 22.97± 2.81; Croubles et al. (2009), 27.7 h; Michiels et al. (1987), 8-48 h.

In summary, in the present study, we found that there was no significant difference between the test product (Fascinil®) and reference product (Flukiver®) in terms of bioavailability, suggesting that two formulations are bioequivalent and that they can be used as interchangeable anthelmintic drugs.

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چکیده

زمینه مطالعه: کلوزانتل یک داروی ضدانگل وسیع الطیف است که به طور گسترده برای کنترل آلودگی های انگلی ناشی از فاسیولا و همونکوس در گوسفند و گاو بکار می رود. **هدف:** مطالعه حاضر به منظور ارزیابی زیست همسنگی فرآورده دارویی فاسینیل (محصول شرکت داروسازی داملران- ایران) در مقایسه با فلاکیور (محصول شرکت داروسازی یانسن- بلژیک) در گوسفند انجام شد. **روش کار:** در یک مطالعه موازی، ۲۸ گوسفند نر ۵-۴ ماهه بطور تصادفی به ۲ گروه تقسیم شدند. گروه اول یک دوز منفرد از سوسپانسیون خوراکی فاسینیل را به عنوان فرآورده آزمون، به میزان ۱۰mg/kgBW، دریافت کردند و گروه دوم همان دوز را از محصول فلاکیور به عنوان فرآورده مرجع دریافت نمودند. نمونه های خون گوسفندان در زمان های صفر، ۴، ۸، ۱۲، ۱۶، ۲۰، ۲۴، ۳۲، ۴۸ و ۷۲ ساعت بعد از تجویز دارو جمع آوری و مقادیر کلوزانتل موجود در پلاسمای آنها با استفاده از یک روش کروماتوگرافی مایع با کارکرد عالی تعیین گردید. با بررسی فارماکوکینتیکی سطوح زیر منحنی غلظت کلوزانتل پلاسمایی- زمان در فاصله ۷۲-۰ ساعت (AUC0-72)، حداکثر غلظت پلاسمایی (Cmax)، و زمان رسیدن به حداکثر غلظت پلاسمایی (Tmax) در گروه های آزمون و مرجع محاسبه و مقایسه گردید. **نتایج:** تفاوت معنی داری بین مقادیر AUC0-72 فرآورده های دارویی فاسینیل و فلاکیور به ترتیب (۶۴۸/۱۸μg.h/mL ± ۲۹۱۳/۰۰ و ۶۲۳/۴۱ ± ۲۹۵۷/۸۸)، حداکثر غلظت پلاسمایی (۷/۷۴μg.h/mL ± ۶۲/۲۲ و ۱۳/۰۳ ± ۷۱/۷۱) و زمان رسیدن به حداکثر غلظت پلاسمایی (۴/۲۸ h ± ۲۳/۳۸ و ۴/۲۸ ± ۲۳/۲۳) وجود نداشت. مقادیر فاصله اطمینان ۹۰٪ نسبت پارامترهای فارماکوکینتیکی گروه آزمون به گروه مرجع در محدوده قابل قبول زیست همسنگی (۱۲۰-۸۰٪) قرار داشتند. **نتیجه گیری نهایی:** فرآورده آزمون (فاسینیل) با فلاکیور زیست همسنگ بوده و آنها را می توان بعنوان داروهای ضد انگل بجای یکدیگر بکار برد.

واژه های کلیدی: زیست همسنگی، کلوزانتل، سوسپانسیون خوراکی، گوسفند

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