Intravascular plasma disposition and salivary secretion of closantel and rafoxanide in sheep

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ABSTRACT

The plasma and salivary disposition of closantel and rafoxanide were examined following intravenous administration in adult sheep. Two studies were conducted with rafoxanide at 7.5 mg/kg and 1 with closantel using 2 doses (5 and 15 mg/kg). The pharmacokinetic profile of both drugs in plasma were best described by a 2-compartmental model with 1st-order rate constants. Plasma disposition of closantel and rafoxanide were characterised by a rapid distribution ($t½_{(\alpha)}$ of <30 min), long elimination half-life ($t½_{(\beta)}$ of 17.0 ± 4.0 days for closantel and 7.2 ± 0.6 days for rafoxanide), small apparent volume of distribution (V_{ss} of <0.15 ℓ/kg) and a slow rate of total body clearance (Cl of <0.01 mℓ/min/kg). The area under the drug plasma concentration curve (AUC) of closantel at 5 mg/kg was nearly twice as large as that of rafoxanide at 7.5 mg/kg resulting from the slower $t½_{(\beta)}$ observed with closantel compared to rafoxanide. Large individual differences were observed in the rate measurements of distribution (k_{12}, k_{21} and $t½_{(\alpha)}$), whereas the parameters of elimination (k_{10}, $t½_{(\beta)}$ and Cl), were more consistent between animals. A dose proportional increase in AUC was observed for closantel administered at 5 and 15 mg/kg. A low, constant salivary concentration of closantel (mean of 0.04 ± 0.05 µg/mℓ) and rafoxanide (mean of 0.07 ± 0.04 µg/mℓ) was observed during the 24-h examination period after dosing.

Key words: closantel, intravenous disposition, rafoxanide, salivary secretion, sheep.

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INTRODUCTION

Halogenated salicylanilides are an important group of anthelmintic agents used for the control of liver fluke and blood-sucking nematodes in sheep and cattle, and larvae of *Oestrus ovis* in sheep. Closantel and rafoxanide are the most widely used of the halogenated salicylanilides and share similar chemical, pharmacokinetic features (extensive plasma protein binding and long elimination half-life), efficacy and safety features[11,17–19]. Rafoxanide concentrations in plasma have been positively correlated with the occurrence of toxicity in lambs[22]. This substantiates the important relationship between the pharmacokinetics of these drugs and their dynamic effects. Apart from a few studies[6,9,13,20–22] not much pharmacokinetic focus has been directed at investigating the absorption and disposition of the halogenated salicylanilides. No intravascular disposition studies have been reported for closantel and rafoxanide.

Substantial amounts of drug may enter into the rumino-reticulum by the saliva[4], which again become available for absorption from the gastrointestinal tract, resulting in recirculation. The secretion of a drug in saliva is dependent on its concentration in plasma, its chemical nature (weak acid or base, and pK_a), and its lipid solubility. Uncharged or lipid-soluble drugs readily appear in the saliva[8]. Acidic drugs with a pK_a of less than the pH of saliva become ionised and accumulate in the alkaline saliva. By this mechanism, some sulphonamides are concentrated in the saliva of ruminants[2]. No studies have been reported that examine the salivary secretion of the halogenated salicylanilides.

The objective of the current study was to evaluate the absolute plasma disposition and salivary secretion of closantel and rafoxanide after intravenous administration to adult sheep.

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MATERIALS AND METHODS

Study design

Three single dose, intravascular (IV-push), disposition studies were conducted with either rafoxanide or closantel in sheep. Two studies (Studies 1 and 2) with rafoxanide consisted each of a single group. Study 1 was a pilot study to determine the basic disposition parameters of rafoxanide using the UV spectrophotometric method of analysis. In Study 2 rafoxanide concentrations were determined by high-pressure liquid chromatography (HPLC) and additional pharmacokinetic observations, such as salivary secretion of rafoxanide, were made.

The 3rd study (Study 3) was a dose proportionality, 2-phase cross-over design with closantel. During phase 1 of the study the intravascular disposition of closantel at the recommended and at 3 times the recommended dose was examined in 2 groups of 2 animals each. Following a washout period of 10 weeks, the intravascular disposition of closantel at the recommended dose rate was studied in all 4 sheep.

Animals

Six, healthy, adult South African mutton merino wethers, aged 1–5 years, were used in the 2 studies with rafoxanide, and four 6-month-old SA mutton merino wethers in the closantel study. Each animal was individually identified by numbered ear-tags. One sheep in Study 2 was stolen during the study period.

Whole blood counts, haematocrit, serum aspartate transaminase activity and serum creatinine, urea and albumin concentrations of all animals, determined at the start of each study, were within the normal ranges expected for sheep[3,16].

Housing and feeding

The studies were conducted in conventional small-stock holding facilities at the Veterinary Faculty, University of Pretoria. Only in the facility used in Studies 2 and 3 were temperature (below 22 °C) and ventilation controlled. All trial animals were housed individually in pens 2 m^2 in

size with concrete floors. Each pen had an automated drinking bowl and feed trough. The sheep were placed into the experimental facilities from 7–26 days before the start of the study to allow for an adaptation period. They were kept in the experimental facilities for the duration of each study.

Chopped lucern hay was fed in the morning every day of the study. Fresh drinking water was available *ad libitum.* Feed was withheld from all animals 12 h before to treatment until 4 h after treatment.

Treatments

Study 1: Rafoxanide 7.5 % m/v injectable solution (Ranide® injectable, MSD, Rahway, New Jersey) at 7.5 mg/kg, i.v.

Study 2: Rafoxanide powder 49.9 % m/m (raw material, Logos AgVet) dissolved in dimethyl sulphoxide (DMSO) at 7.5 mg/kg, i.v.

Study 3: Closantel powder 98 % m/m (raw material, Smith Kline Beecham) dissolved in DMSO at 5 mg/kg and 15 mg/kg, i.v.

Intravenous treatment was administered by slow injection into the jugular vein over *c.* 0.5 min. Rafoxanide or closantel powder were dissolved in a sterile intravascular solution of DMSO (DMSO 98 %, Kyron) at a concentration to achieve an intravascular dose of 1 mℓ/10 kg. All dose sizes were calculated according to body mass measured on the day or day before treatment.

Blood samples

Venous blood was collected in 10 mℓ heparinised vacuum tubes, immediately before treatment and at 0.5, 1, 3, 5, 6, 12, 18, 24, 30, 36, 48 and 60 h, and 3, 5, 7, 9, 11 14, 21 28 and 35 days after treatment for Study 1 and 5 min, 15 min, 0.5, 1, 2, 3, 5, 7, 9, 12, 15, 18, 24, 30, 36 and 48 h, and 3, 5, 7, 10, 14, 21 28, 35, 42, 49, 56 and 63 days for Studies 2 and 3. Timed collection occurred within 30 sec of the scheduled time up to 24 h, and thereafter within 1–5 min.

Blood samples were centrifuged at 3000 r.p.m. for 15 min and the plasma collected. Two equal aliquots of plasma from each animal were transferred into clean polycarbonate tubes and stored at –20 °C until analysed. Recovery and storage of plasma occurred within 12 h of blood collection.

Mixed saliva samples

Mixed gland saliva (2–4 mℓ) was collected by aspiration from the back of the pharyngeal area using a disposable plastic 10 mℓ syringe to which a length (150 mm) of soft plastic tubing was attached. Samples were collected just before treatment, and at 1, 3, 7, 12, 18 and 24 h after treatment.

The saliva was centrifuged at 3000 r.p.m. for 15 min, the supernatant transferred to clean polycarbonate tubes and the sample stored at –20 °C until analysed.

Rafoxanide and closantel analyses

Rafoxanide plasma concentrations in the pilot study (Study 1) were determined by a spectrophotometric method, while rafoxanide and closantel concentrations in plasma and saliva were measured by HPLC in Studies 2 and 3, respectively. The accuracy, precision, sensitivity and repeatability of both analytical methods used were adequately validated according to the method described by M Mülders and co-workers (Department of Pharmacology and Toxicology, Faculty of Veterinary Science, University of Pretoria, pers. comm., 1998).

Rafoxanide concentrations were determined individually and in a pooled sample of saliva collected from sheep in Study 2.

Pharmacokinetic analysis

Non-linear compartmental analysis of the rafoxanide plasma data was performed by PC Nonlin Version 4.2 (Statistical Consultants, New York) computer programme using the Nelder-Mead algorithm[14]. Initial pharmacokinetic parameter estimates, used for the non-linear analysis, were derived automatically by initial linear analysis performed by the programme.

Akaike's information criterion[23], based upon the mean values of the final estimates of the associated pharmacokinetic parameters and lack of systematic deviations around the fitted disposition curve, was used to determine the number of exponential terms that best described the data.

Primary pharmacokinetic parameters for all 3 studies were derived from a 2-compartmental analysis with IV-push input, 1st-order output using macroconstants as primary parameters, yielding the microconstants (k_{10}, k_{12} and k_{21}), the partial exponents (α and β) and the coefficients (A and B). Secondary disposition parameters, including area under the drug plasma concentration *versus* time curve (AUC), distribution half-life ($T½_{(\alpha)}$), elimination half-life ($T½_{(\beta)}$), elimination constant half-life (k_{10}-HL), total body clearance (Cl), volume of the central compartment (V_c'), apparent volume of distribution at steady-state (V_{ss}), area under the 1st-moment curve (AUMC) and mean residence time (MRT), were derived from the primary parameters. Total plasma concentration of rafoxanide and closantel at zero time (Cp^0) was calculated as the sum of the coefficients (A + B).

Descriptive statistics (mean ± SD) were calculated for all pharmacokinetic parameters within each study. Differences in the mean pharmacokinetic parameters were statistically compared using the Student's *t*-test, whereas the nonparametric Wilcoxon Rank Test was applied to the rate constants (k_{01} and k_{10}), rate constant half-lives (k_{01}-HL and k_{10}-HL), t_{max} and t_{lag}. All statistical procedures were performed using the SAS statistical software programme for Windows 95[1].

RESULTS

The plasma concentration *versus* time profile data after IV-push for rafoxanide (Studies 1 and 2) (Fig. 1) and closantel (Study 3) (Fig. 2) were best described by a 2-compartmental open model with 1st-order rate constants. A coefficient of determination percentage (r^2) of >98 % for best fit of the disposition curve was obtained in all cases.

Similar pharmacokinetic results of rafoxanide were obtained in Studies 1 and 2 (Table 1). There were no significant ($P > 0.05$) differences between the 2 studies for all pharmacokinetic parameters. The pharmacokinetic data of closantel at 5 and 15 mg/kg indicate a dose proportionality (Table 2).

Similarities and differences were noted for the disposition of closantel and rafoxanide (Tables 1 and 2). For both drugs the rate constants of distribution from (k_{12}) and to (k_{21}) the central compartment were similar. A slight increase in plasma concentrations of both drugs occurred 18–48 h after administration. Both drugs showed a short $t½_{(\alpha)}$, long $t½_{(\beta)}$ and MRT, and small V_c, V_{ss} and Cl. At the recommended dose rates rafoxanide had a significantly ($P < 0.05$) shorter $t½_{(\alpha)}$, longer $t½_{(\beta)}$ and MRT, smaller V_{ss} and more rapid Cl than closantel. The AUC of closantel administered at 5 mg/kg was nearly twice as large as that of rafoxanide that was administered at 7.5 mg/kg. Cp^0 of rafoxanide, on the other hand, was higher than that of closantel, reflecting the dose difference. Large individual differences were observed in the rates of distribution for both drugs, whereas in the case of parameters of elimination the results were more consistent between animals.

A low, variable concentration of both closantel (0.04 ± 0.05 µg/mℓ) and rafoxanide (0.07 ± 0.04 µg/mℓ) was present in the saliva during the 24 h period of examination after treatment at the recommended dose rates of 5 mg/kg and 7.5 mg/kg, respectively (Table 3). A similar harmonic mean concentration (µg/mℓ) of rafoxanide content in a pooled sample

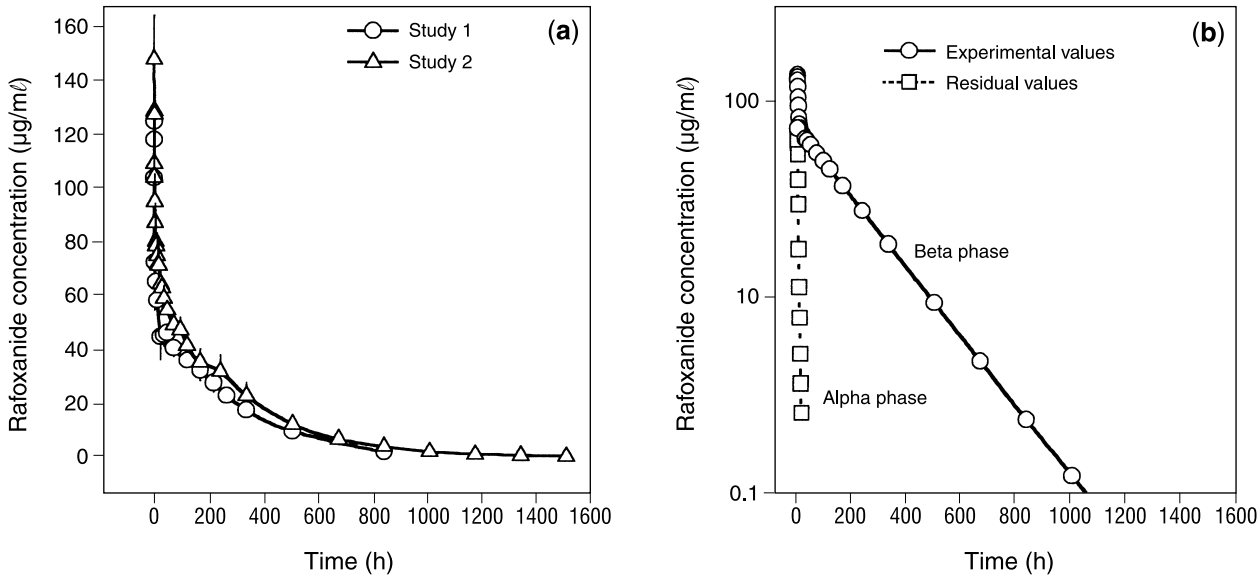

Fig. 1: (a) **Mean plasma concentration *versus* time data of rafoxanide at 7.5 mg/kg in Study 1 and 2 and** (b) **a semilogarithmic plot of plasma data from Study 2 describing the intravascular disposition of rafoxanide in sheep.**

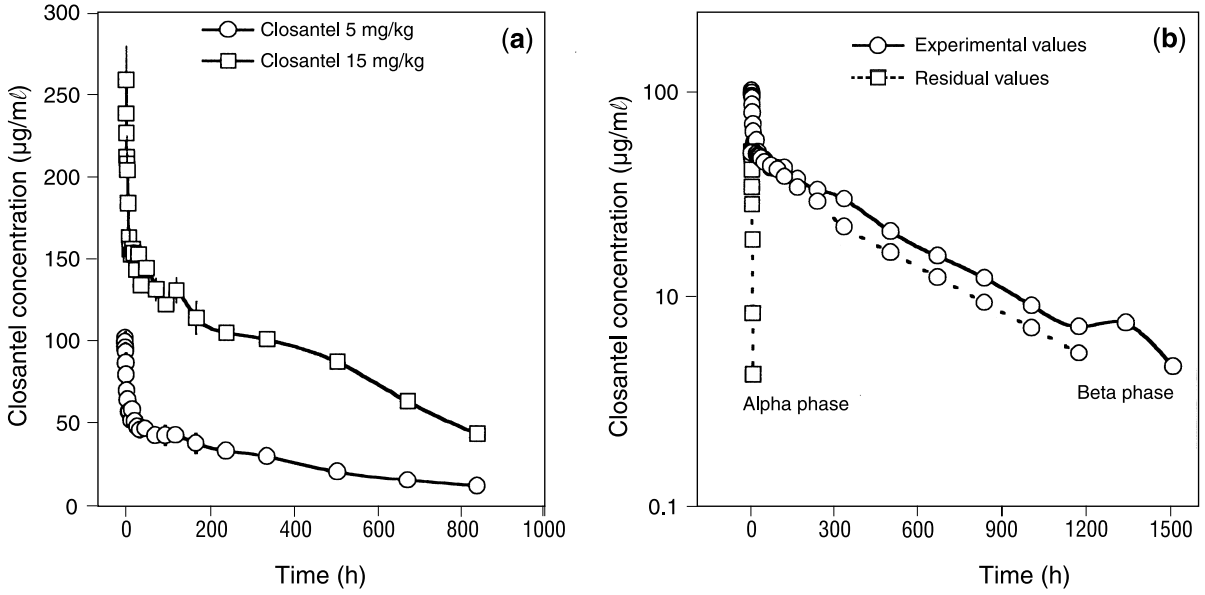

Fig. 2: (a) **Mean plasma concentration *versus* time data of closantel at 5 mg/kg and 15 mg/kg and** (b) **a semilogarithmic plot of plasma data describing the intravascular disposition of closantel at 5 mg/kg in sheep.**

(6 mℓ) of all animals was observed as compared to the harmonic mean of the individual animals. The mean saliva concentration of closantel at 15 mg/kg was markedly higher (×6) than after the recommended dose (5 mg/kg).

DISCUSSION

Pharmacokinetic studies in ruminants with closantel and rafoxanide have previously been conducted with oral, intraruminal (i.r) and intramuscular (i.m.) administration[9,12,13]. This study reports for the 1st time the pharmacokinetics of closantel and rafoxanide administered intravenously (i.v.) in sheep. Intravascular disposition of both drugs was characterised by a rapid distribution, small apparent volume of distribution, slow elimination and small total body clearance. The dose-proportional pharmacokinetics of closantel at 5 and 15 mg/kg suggest that the pharmacokinetic processes of these compounds are 1st-order and are therefore not saturated at the recommended dose rates. Michiels *et al.*[12] reported that the oral absorption of closantel is also dose-dependent. A linear increase in closantel plasma concent rations was observed in sheep and cattle at doses between 2.5 mg/kg and 10 mg/kg. Similar 1st-order kinetics have been reported for rafoxanide[22]. A small recirculation of closantel and rafoxanide to the central compartment, observed as a slight increase in plasma concentrations 18–48 h after treatment, is most likely caused by an enterohepatic circulation that has been described for this group of drugs[5,12]. Although recirculation of these compounds to and from the gastrointestinal tract, in particular the rumino-reticulum, and recirculation through salivary secretion, may also play a role. The exponents of the 2-compartmental model, which best described the intravascular pharmacokinetic profiles of closantel and rafoxanide, probably depict the initial rapid rate of distribution followed by a slower rate of elimination. However, according to Mohammed-Ali and Bogan[13], the pharmacokinetic profiles of orally-administered rafoxanide, closantel and oxyclozanide are best described by a tri-exponential equation. These authors suggest that the elimination phase may be divided into a rapid

Table 1: **Mean pharmacokinetic parameters describing the plasma disposition of rafoxanide in sheep after intravascular administration in Studies 1 and 2.**

Parameter	Mean ± SD	
	Study 1 (n = 6)	Study 2 (n = 5)
AUC (µg/h/mℓ)	16364 ± 2130	18203 ± 1932
Cp^0 (µg/mℓ)	132.5 ± 16.5	138.7 ± 16.1
k_{10} (per h)	0.0082 ± 0.0010	0.0076 ± 0.0005
k_{12} (per h)	0.2593 ± 0.1595	0.1810 ± 0.0741
k_{21} (per h)	0.1745 ± 0.0754	0.2068 ± 0.0864
a (per h)	0.44 ± 0.23	0.39 ± 0.16
β (per h)	0.0033 ± 0.0003	0.0040 ± 0.0003
k_{10}-HL (h)	86.2 ± 10.9	91.2 ± 6.2
$t½_{(\alpha)}$ (h)	1.89 ± 0.63	2.16 ± 1.01
$t½_{(\beta)}$ (d)	8.8 ± 0.9	7.2 ± 0.6
V_c (ℓ/kg)	0.057 ± 0.007	0.055 ± 0.006
V_{ss} (ℓ/kg)	0.138 ± 0.0070	0.102 ± 0.010
Cl (mℓ/min/kg)	0.0078 ± 0.001	0.0069 ± 0.0007
MRT (d)	12.5 ± 1.4	10.3 ± 0.9
r^2 %	99.2 ± 0.9	99.0 ± 0.5

Table 2: **Mean pharmacokinetic parameters describing the plasma disposition of closantel in sheep after intravascular administration in Study 3.**

Parameter	Doses administered	
	5 mg/kg (n = 6)	15 mg/kg (n = 2)
AUC (µg/h/mℓ)	30077 ± 8063	113624 (110.518–116729)
Cp^0 (µg/mℓ)	101.6 ± 7.9	245.4 (233.2–259.6)
k_{10} (per h)	0.0036 ± 0.0009	0.0022 (0.0021–0.0022)
k_{12} (per h)	0.0971 ± 0.0247	0.0893 (0.0787–0.0999)
k_{21} (per h)	0.0983 ± 0.0173	0.1420 (0.1356–0.1483)
a (per h)	0.1972 ± 0.0409	0.2321 (0.2151–0.2491)
β (per h)	0.0018 ± 0.0004	0.0013 (0.0013–0.0013)
k_{10}-HL (h)	205.4 ± 53.7	3.0 (2.8–3.2)
$t½_{(\alpha)}$ (h)	3.7 ± 0.8	321.5 (311.6–331.3)
$t½_{(\beta)}$ (d)	17.0 ± 4.0	21.9 (21.8–21.9)
V_c (ℓ/kg)	0.049 ± 0.003	0.062 (0.058–0.065)
V_{ss} (ℓ/kg)	0.098 ± 0.005	0.100 (0.097–0.103)
Cl (mℓ/min/kg)	0.0030 ± 0.0007	0.0022 (0.0022–0.0023)
MRT (d)	24.2 ± 5.7	31.4 (31.4–31.5)
r^2 %	99.4 ± 0.4	98.9 (98.8–98.9)

Table 3: **Mean concentration of closantel and rafoxanide in saliva.**

Time after	Mean ± SD concentrations in saliva (µg/mℓ)			
	Closantel		Rafoxanide	
treatment (h)	5 mg/kg (n = 6)	15 mg/kg (n = 2)	7.5 mg/kg (n = 6)	Pooled sample
1	0.02 ± 0.03	0.27	0.05 ± 0.03	0.14
3	0.03 ± 0.03	0.23	0.03 ± 0.01	0.05
7	0.08 ± 0.16	0.41	0.08 ± 0.07	0.12
12	0.08 ± 0.06	—	0.07 ± 0.04	0.13
18	0.05 ± 0.05	0.25	0.10 ± 0.05	0.22
24	0.05 ± 0.05	0.16	0.19 ± 0.13	0.27
Mean*	0.04	0.24	0.07	0.07
SD	0.05		0.04	

*Harmonic mean.

mixed distribution-elimination phase and a slower true, metabolism-elimination phase. In their study, plasma concentrations were measured up to 105 days post-treatment, which may account for the additional exponent of elimination compared to the current investigation, in which plasma concentrations were measured up to 63 days. It is doubtful whether metabolism would have contributed significantly to the slower elimination phase[13], since both closantel and rafoxanide are poorly metabolised and excreted mainly unchanged[7,12]. Extensive plasma binding[9,12,13], rumino-reticulum recirculation and salivary secretion are more likely responsible for the longer persistence of these compounds in the body. Although only very low concentrations (0.04–0.07 µg/mℓ) of closantel and rafoxanide were secreted in saliva during the 24-h examination period following treatment, the total amount of drug secreted into the rumino-reticulum may be considerable when taking into consideration the volume of saliva secreted per day and the long mean residence time (300–600 h) of these compounds in the body. The daily secretion of saliva in sheep is estimated at 6–16 ℓ/d, depending on the type and nature of the diet[10]. Therefore, over 24 h, between 0.24 and 11.2 mg of drug, representing up to 5 % of the total dose in an adult sheep, can potentially be secreted into the rumino-reticulum. The reason for the proportionally greater (×6) secretion of closantel in saliva following 15 mg/kg than after 5 mg/kg is unknown. It suggests that saturation of plasma binding had occurred at the higher doses, although according to Prichard[15] rafoxanide will dissolve into plasma up to 2 mg/mℓ.

Salicylanilides are weak organic acids that may become ionised and accumulate in the alkaline saliva. On the other hand, the extensive plasma binding of these drugs will limit the amount of free drug available for secretion by saliva and account for the low concentrations observed. Closantel and rafoxanide added to the rumino-reticulum by salivary secretion will become more non-ionised in the more acidic environment and may either readily diffuse across the rumen membrane or be delivered to the abomasum and lower gastrointestinal tract, where further absorption may occur. This addition of drug into the rumino-reticulum by salivary secretion, as well as potentially by direct diffusion of drug across the forestomach membrane, and reabsorption from this compartment, will result in recirculation and contribute to the persistence of closantel and rafoxanide in ruminants. Further studies are required to establish the importance of salivary secretion after oral administration.

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