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Clinical pharmacology of clemastine in healthy dogs

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Abstract The pharmacokinetic properties of clemastine were investigated in six healthy dogs and compared with the effect of the drug recorded as inhibition of wheal formation induced by intradermal injections of histamine. Clemastine clearance was high (median: 2.1 L h^{-1} kg^{-1}) and the volume of distribution large (13.4 L kg^{-1}). The half-life after intravenous administration was 3.8 h and the plasma protein binding level *in vitro* was 98%. After oral administration, the bioavailability was only 3%. Given intravenously, clemastine (0.1 mg kg^{-1}) inhibited wheal formation completely for 7 h, whereas the effect after oral administration (0.5 mg kg^{-1}) was minor. The data show that most dosage regimens suggested in the literature for the oral administration of clemastine to dogs are likely to give too low a systemic exposure of the drug to allow effective therapy.

Keywords: clemastine, dog, histamine, LC-MS/MS, pharmacokinetic, wheal.

INTRODUCTION

Antihistamines are used widely in veterinary medicine for the treatment of canine atopic dermatitis (CAD) either together with hyposensitization or, more seldom, as the sole therapy.[1–7] Administration of antihistamines has also been reported to reduce the dosage of systemic glucocorticoids required to control pruritus in some dogs.[8,9] Individual differences in response to antihistamines are reported in dogs. Usually an 'antihistamine trial' is performed to determine which antihistamine is the most effective in the individual patient. Commonly, three to five different antihistamines are used, each given consecutively for two weeks.[1,2,10,11]

The antihistamines most frequently used in small animal dermatology are H_1-receptor antagonists that competitively inhibit histamine at the receptor sites on cell membranes. H_1-antagonists have classically been used for the treatment of hypersensitivity conditions and urticaria, to antagonize the effect of histamine released from degranulating mast cells. In allergic and hypersensitivity reactions, allergens cross-bind immunoglobulin (Ig)E on the surface of mast cells, thereby causing degranulation of the cells. Histamine is one of the inflammatory mediators released together with proteolytic enzymes, prostaglandins, leukotrienes and pro-inflammatory cytokines. Intradermally injected, histamine causes a local oedema (wheal) with surrounding erythema, visible on white skin.[12]

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Clemastine belongs to the first generation of antihistamines. It is an aminoalkylether, a lipid-soluble compound that passes through the blood–brain barrier.[13] The response rate varies between studies depending on the study design but seems to be rather low.[6,7,14,15]

Clemastine is also used for hypersensitivity reactions in humans.[13,16,17] Only recently has information on the pharmacokinetics of clemastine in humans been available due to the high potency of the drug and accordingly difficulties in the analysis of drug concentrations in plasma.[18]

To our knowledge, the pharmacology of clemastine in the dog is mostly unknown. The aim of this study was to increase the basic knowledge about the pharmacology of the drug in the dog. This antihistamine was chosen as it is well known among Swedish veterinarians and is available on the Swedish market (as Tavegyl®) for both intravenous and oral administration.[19] Moreover, in Sweden, clemastine is one of the antihistamines usually included in the protocol to control pruritus in atopic disease in the dog. The second generation of antihistamines used in human medicine, which do not pass through the blood–brain barrier, has not proven effective in dogs with allergic pruritus.[1,7,20]

In order to assess antihistamine activity, basic pharmacokinetic parameters of clemastine were calculated after intravenous and oral administration, respectively.

Plasma concentrations of clemastine were compared with the effect of the drug, recorded as the inhibition of wheal formation induced by intradermal injections of histamine.

MATERIALS AND METHODS

Animals

The study comprised six clinically healthy female Beagles, with no history or signs of skin disease. They were born and housed at the Department of Small Animal Clinical Sciences, Uppsala. Their mean age was 5.8 years (range 4–10.5 years) and their mean body weight 12.6 kg (range 12.2–13.1 kg). None of the dogs had received any medication for at least four weeks before the study. Care of the animals and the experimental design were approved by the local ethics committee in Uppsala, Sweden.

Drug administration

The Beagles received clemastine orally and intravenously using a crossover study design. The dogs were divided into two groups, with one group receiving the drug first orally, then after a washout period of 21 days, intravenously. The remaining dogs started with the intravenous dose. One of the dogs was excluded from oral administration due to illness (unrelated to the study).

Clemastine fumarate (Tavegyl® solution for injection 1 mg mL^{-1}, Novartis, Stockholm, Sweden) was used for intravenous administration at a dose of 0.1 mg kg^{-1}. This was given diluted in 20 mL of saline solution (0.9% NaCl) and administered slowly into the cephalic vein over a period of 10 min. Clemastine fumarate (Tavegyl® tablets, 1 mg) at a dose of 0.5 mg kg^{-1} was given for oral administration. The dogs were kept under constant observation for several hours during and after drug administration. No dog showed any clinical sign of adverse effects from the drug. The dogs were not fed for at least 10 h before and 4 h after the drug administration.

Results from a pilot study had shown that the doses chosen were adequate to allow quantification of the drug in plasma (data not shown).

Blood sampling

Blood samples were collected from a cephalic vein catheter (a different vein from that used for the infusion) before and 10, 15, 20, 30, 45, 60, 75 and 90 min and 2, 3, 4, 7, 12, 16 and 23 h after the start of the intravenous drug infusion. Blood was also collected before and 15, 30, 45, 60, 75 and 90 min and 2, 3, 4, 5, 7, 12, 16 and 23 h after oral administration. The blood was collected in heparinized test tubes and was centrifuged at 600 ***g*** for 10 min. The plasma was separated and frozen at –20 °C.

Recording of the pharmacodynamic effect

The antihistamine effect from clemastine was recorded using an intradermal test. Unsedated dogs were placed in lateral recumbence. The lateral chest behind the elbow was shaved with electric clippers and the exposed skin was not washed prior to injecting.

Intra-dermal injections with 7 μg per site (0.07 mL) histamine hydrochloride (0.1 mg mL^{-1}, ex tempore, Apoteket AB, Sweden) were given using 27-gauge needles. After 15 min the diameter of the skin reaction was measured. Testing was performed at 0.5, 1, 2, 4, 7, 12 and 23 h after intravenous and oral administration. Sterile saline (0.07 mL) served as a negative control (a mean value for all dogs was calculated from 21 administrations).

For each dog and time point, the areas of the wheal and the erythema, respectively, were calculated from the mean value of the two diameters measured. When calculating the wheal area, the mean area of the saline wheals was subtracted. The mean wheal area at each time point was compared with the mean area measured before administration of the drug using ANOVA and Dunnett's post hoc test. The null-hypothesis was rejected if $P < 0.05$. The software used was MINITAB 13 for Windows (Mininc, State College, PA, USA).

Measurement of the plasma protein binding level

Binding of clemastine to canine plasma proteins was determined by means of equilibrium dialysis, using semipermeable membranes (MWCO 12–14 000, Spectrapor, Spectrum Medical Industries Inc, Los Angeles, CA, USA). Plasma samples were adjusted to a pH of 7.4 with 1 mol L^{-1} HCl (8–10 μL mL^{-1} of plasma), and 1 mL of plasma from each of the six dogs was dialysed against 1 mL of buffer solution (28 mmol L^{-1} Na_2HPO_4, 5.6 mmol L^{-1} NaH_2PO_4 and 38 mmol L^{-1} NaCl, pH 7.4) containing 100 ng of clemastine per mL at 37 °C for 4 h. The fraction of drug bound to plasma proteins was calculated as the ratio between the bound fraction (i.e. the difference between drug concentration in plasma and the unbound fraction in the buffer solution) and drug concentration in plasma. Pooled plasma and buffer from two dialysis cells of each were used for the analysis and the experiment was repeated three times for each dog. Results of preliminary tests indicated that equilibrium was reached before 3 h of dialysis, and that no differences in protein binding were detected for plasma clemastine concentrations ranging from 10 to 300 ng mL^{-1}.

Analysis of clemastine concentrations

Chemicals. Clemastine hydrogen fumarate was obtained from Novartis Pharma AG (Basel, Switzerland). Orphenadrine citrate was from Sigma (St Louis, MO, USA). The water was of Millipore quality (Millipore, Bedford, MA, USA). All other reagents were of analytical grade or better and used without further purification. Blank canine plasma was obtained from healthy dogs at the Department of Small Animal Clinical Sciences, Uppsala.

Sample pre-treatment. The sample pre-treatment method was slightly modified from Törneke *et al*. 2003.[21] The plasma samples and the samples from both compartments of the equilibrium dialysis chambers were pretreated in the same way: 100 μL of the internal standard orphenadrine (containing 3.1 ng orphenadrine base

for the plasma samples and 3.4 ng for the protein binding study), 4 mL of hexane/dichloromethane 4 : 6 and 1 mL of 0.1 M NaOH were added to ≈ 1 mL of each plasma sample or each sample from the equilibrium dialysis study (the volume of every sample was measured using a volumetric pipette). The samples were mixed for 15 min and centrifuged for 10 min at 2300 ***g***. The supernatant was removed and evaporated to dryness under a stream of nitrogen at ≈ 60 °C. The residues were reconstituted in 100 µL of 40% methanol and 60% 0.1 M acetic acid in water.

Calibration and validation. Standards for the calibration curve were prepared by adding varying amounts of clemastine to blank plasma. Two different concentration intervals in the calibration curve were used for the plasma study depending on the concentration in the sample: 0.048–10.2 and 10.2–96.6 ng clemastine base per mL plasma, respectively. In the protein binding study, a calibration curve interval of 0.058–235 ng mL^{-1} was used. The calibration curves were constructed by linear regression of peak area ratios of clemastine to internal standard as a function of clemastine concentration. Quality control samples were prepared by spiking blank plasma with clemasine standard from a separate weighing, at 0.44, 6.6 and 44.2 ng clemastine per mL, for evaluation of the accuracy and precision of the method. The standards and the quality control samples were treated in the same way as the samples (see above).

Liquid chromatography tandem mass spectrometry. The reconstituted samples were quantified with liquid chromatography electrospray tandem mass spectrometry (LC-ESI-MS/MS) using a HP1100 liquid chromatograph with a binary pump (Hewlett-Packard, Waldbronn, Germany) and a Luna C_{18}2(Phenomenex, Torrance, CA, USA) chromatographic column (length 150 mm, inner diameter 2.00 mm and particle diameter 5 µm) or a Luna $C_8$2(length 50 mm, inner diameter 2.00 mm and particle diameter 5 µm). The samples were eluted isocratically with a mobile phase composition of 52% aqueous formic acid (0.05%) and 48% methanol. The injection volume was 5.0 µL and the volumetric flow rate 0.2 mL min^{-1}. Chromatography was performed at ambient temperature.

A Quattro LC (Micromass, Manchester, UK) quadrupole–hexapole–quadrupole mass spectrometer with an electrospray interface (ESI) was connected to the column outlet. The software MASSLYNX 3.3 was used for instrument control and data acquisition. The mass spectrometer was tuned for optimal parameter settings in the same way as in the earlier study.[21] The chromatograms were obtained in Selected Reaction Monitoring (SRM) mode, switching between the transitions *m*/*z* 344 → 215 for clemastine and 269.5 → 180.5 for orphenadrine.

Pharmacokinetic calculations. The plasma concentration vs. time profile for clemastine in each individual was analysed using noncompartmental methods based on statistical moment theory.[22] A commercially available software program was used (WINNONLIN STANDARD, Pharsight Corporation, Palo Alto, CA, USA). The rate constant associated with the elimination phase (λ) was estimated by means of linear regression on data sets where a linear phase (on a log scale *y*-axis) was well defined ($r^2 \geq 0.9$) and covered a large part of the area under the plasma concentration vs. time curve (AUC). From λ, the elimination half-life ($t_{1/2}$) was calculated. Lambda was also used to extrapolate AUC and the area under the first moment curve (AUMC) to infinity. From AUC and AUMC, clearance (Cl), mean residence time (MRT) and volume of distribution at steady state (Vd_{ss}) were calculated. The oral bioavailability (*F*) was calculated from the AUC from 0 to the last time point measured ($AUC_{23\ h}$) using the equation:

$$F\,(\%) = 100 \times (AUC_{oral,\ 23\ h} \times dose_{iv})/(AUC_{iv,\ 23\ h} \times dose_{oral})$$

Table 1. Validation data

Spiked concentration of quality control sample (ng mL^{-1})	Accuracy (%)	RSD (%) (n = 3)
Day 1		
0.44	93	18.8
6.6	114	8.78
44.2	104	3.96
Day 2		
0.44	108	4.02
6.6	96	1.82
44.2	108	1.50
Day 3		
0.44	122	1.95
6.6	97	8.32
44.2	114	4.59
Day 4		
0.44	107	12.7
6.6	101	3.26
44.2	116	2.67
Between-day precision		RSD (%) (n = 4)
0.44		11.1
6.6		8.0
44.2		4.76

RESULTS

Analytical method validation

Quality control samples were analysed together with each group of real samples. The precisions expressed as the relative standard deviation (RSD) and the accuracies are presented in Table 1. The standard curves were linear with correlation coefficients (r^2) in the range 0.983–0.999.

Pharmacokinetics

The plasma concentration of clemastine vs. time profiles, after intravenous and oral administrations, respectively, are presented in Fig. 1. At the first time points measured after intravenous administration, a distribution phase with rapidly declining plasma concentrations was evident in all animals but one. From 2 to 12 h the decline followed

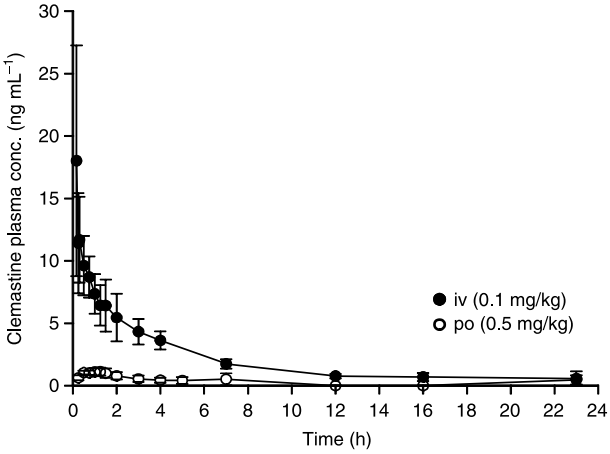

Figure 1. Mean (± SD) plasma concentration of clemastine after intravenous (n = 6) and oral (n = 4) administration.

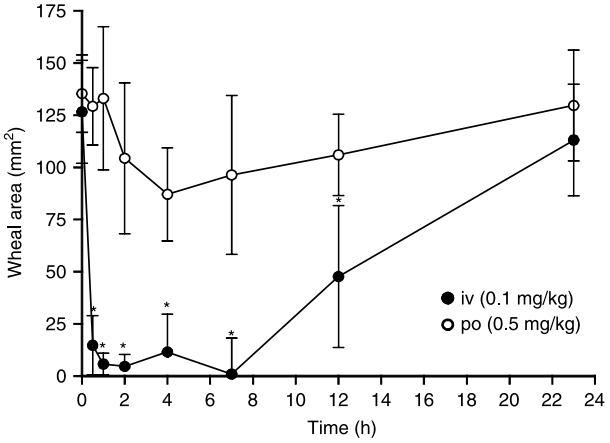

Figure 2. Mean (± SD) histamine-induced wheal areas after intravenous (n = 6) and oral (n = 4) administration of clemastine. The mean area of the saline induced wheals is subtracted from each of the areas. The stars represent significant differences compared to baseline (ANOVA, $P < 0.0001$).

Table 2. Pharmacokinetic parameters (median, range) in plasma following clemastine administration intravenously (0.1 mg kg^{-1}, n = 6) and orally (0.5 mg kg^{-1}, n = 4) to Beagle dogs. For explanations of the abbreviations, see Materials and methods

Parameter	Median	Range
$AUC_{inf,\ iv}$ (ng mL^{-1} h)	47	39–66
$AUC_{extr,\ iv}$ (%)	4.5	3.8–13.0
Cl (L h^{-1} kg^{-1})	2.1	1.5–2.6
Vd_{ss} (L kg^{-1})	13.4	10.7–21.0
MRT (h)	6.7	4.6–10
λ_{iv} (L h^{-1})	0.18	0.16–0.29
$t_{1/2\ \lambda,\ iv}$ (h)	3.79	2.3–4.4
$AUC_{23\ h,\ oral}$ (ng mL^{-1} h^{-1})	7.9	3.1–13.6
F (%)	2.9	1.1–5.8
Plasma protein binding level (%)	98.2	97.8–98.4

a single exponential pattern, allowing for λ being determined (r^2 = 0.91–0.99, median value 0.98).

After oral administration, the plasma concentrations were low and variable. C_{max} was ≈ 1 ng mL^{-1} and the absorption rapid (Fig. 1). No well-defined λ-phase was found in any of the dogs due to the low exposure. In dog 2, a pre-administration plasma concentration of clemastine (2.2 ng mL^{-1}) was found. This dog was excluded from further analysis. The main pharmacokinetic parameters for clemastine are presented in Table 2.

Intradermal test

After intravenous administration, a prominent drug effect was seen. The effect duration was ≈ 12 h (Fig. 2). For the first 7 h, the size of the wheals was similar independent of whether histamine or saline was used. The area of the surrounding erythema however, was not reduced during clemastine exposure. The drug effect seen after oral administration was minor and not statistically significant (P = 0.129).

DISCUSSION

The aim of this study was to increase the basic knowledge about the pharmacological properties of clemastine in the dog. Clemastine is one of several antihistamines commonly recommended for the management of canine atopic disease. However, antihistamines have never been found to be completely effective in dogs. As there seems to be considerable interindividual differences in response to antihistamines in dogs, an 'antihistamine trial' is usually performed.[1,2,10,11,15] Clemastine is often included in such trials,[1,2,6,10,15] although the pharmacological properties of the drug in dogs are mostly unknown. To our knowledge, neither pharmacokinetic studies (showing the systemic exposure of the drug) nor dose finding studies (showing the optimal dose to be used) have been performed.

The dose regimen recommended for oral treatment with clemastine in dogs varies considerably, from 0.05 to 0.1 mg kg^{-1} twice daily[1,2,6,7,9,11,23–25] to, in a few reports, 0.5–1.5 mg kg^{-1} twice daily.[10,15] The dose recommended for humans is 0.025 mg kg^{-1}.[19] In our study, clemastine was administered intravenously and orally on two different occasions. After intrvenous administration (0.1 mg kg^{-1}), a prominent drug effect (as measured by inhibition of wheal formation after intracutanous histamine provocation) was seen, with a duration of ≈ 12 h. This resembles the findings reported from studies in humans.[19,26,27]

Although the dose given orally in this study (0.5 mg kg^{-1}) was in the upper range of those recommended for dogs, and considerably higher than that used in most studies,[1,2,6,7,9,11,23–25] the drug effect after oral administration was minor and not statistically significant. It seems like a prominent antihistamine effect can be obtained in dogs using clemastine, but the doses needed, if administered orally, are very high compared with the doses approved for humans. This finding is consistent with findings in horses where the drug response after oral administration was minor although a high dose was used.[21]

Interspecies variation in drug response may depend on pharmacokinetic, pharmacodynamic or

pathophysiological differences between the species investigated. The intradermal test used in this study is well established as an experimental model to show effect from antihistamines.[17,21,28–30] Our data from the intravenous administration show that this model is also valid for clemastine in the dog. We believe that the interspecies difference in drug response is mainly of pharmacokinetic origin.

The plasma kinetic data of clemastine in dogs reveal that the oral bioavailability was low, between 1 and 6%, similar to the 3.4% reported recently to be the oral bioavailability of clemastine in horses.[21] This is considerably lower than the 20–70% estimated for humans.[18] The data are not really comparable as the human data are estimated from oral administration of the drug only, but it can be concluded that one prominent difference between humans, on the one hand, and dogs and horses, on the other hand, is in the uptake and/or first passage metabolism of oral clemastine. The plasma concentrations obtained in studies of the three species were rather similar although the doses given differed considerably (0.025, 0.2 and 0.5 mg kg^{-1}, respectively, for humans, horses and dogs, respectively).[18,21]

Although the dose was selected to give the same plasma concentrations in dogs as in humans after administration of the approved dose, there was a difference in the pharmacological response. Clemastine was found to be effective in humans with a maximal plasma concentration (C_{max}) of 0.7 ng mL^{-1} and a total exposure (AUC) of 13 ng mL^{-1} h^{-1}.[18] In dogs (and horses) the effect recorded was minor (C_{max}:2.7 and ≈ 1 ng mL^{-1}, AUC: 8.5 and 7.9 ng mL^{-1} h^{-1} for horses and dogs, respectively).[21] One possible explanation for this may be interspecies variation in drug distribution to the skin. The plasma protein binding level in dogs was 98% and the corresponding figure in horses 99%.[21] Thus, only a small fraction of the drug in canine or equine plasma is free and available for distribution to peripheral tissues. To our knowledge, the protein binding level of clemastine in humans has not been investigated. In addition, pH might influence the distribution of drugs. Clemastine is a tertiary amine and thus a weak base. Therefore, it is likely to accumulate in body compartments with low pH. Human skin is such a compartment (pH 4.8), whereas dog skin has a pH resembling that in plasma and is therefore not a likely compartment for clemastine accumulation.[31]

H_1-receptor antagonists are known to have an antioedematous action[29,32] and thus reduction of the wheal area obtained after intradermal injection of histamine is a reliable marker for antihistaminic effect in the skin. In the present study, a maximal effect was seen for 7 h after intravenous administration. The area of the surrounding erythema, however, was not reduced during clemastine exposure. This finding is in accordance with those reported by Kurata *et al.*[33] who studied the wheal and erythema formation after intradermal injections with a fluoroquinolone. As in our study, wheal formation was inhibited with an H_1-antagonist but the erythema remained. However, the erythema could be inhibited with an H_2-antagonist. Several studies have reported that giving an H_2-antagonist in addition to an H_1-antagonist may enhance the wheal and erythema suppression in humans. A possible explanation for this phenomenon is the fact that skin blood vessels possess histamine H_2-receptors. It is via these receptors that histamine mediates a dilation of the vessel, an action that can be inhibited by H_2-receptor antagonists.[17,27,33–35] Whether H_2-receptor antagonists in combination with H_1-receptor antagonists could be of clinical interest in the treatment of canine atopic disease is not known. However, treatment with H_2-receptor antagonists alone appears to be ineffective in dogs with allergic skin disease.[2,5]

In conclusion, our data show that most dosage regimens suggested in the literature for oral administration of clemastine to dogs is likely to give too low a systemic exposure of the drug to allow effective therapy. Because of the low oral bioavailability of the drug, clemastine can only be recommended for oral control of hypersensitivity conditions in dogs if administered in very high doses (probably 1 mg kg^{-1} twice daily, or more) and thus the usefulness of the drug in dogs might be limited. Further dose-finding studies would be necessary to determine if clemastine is a suitable drug for treatment of allergic conditions when used in such high doses.

However, after intravenous administration of clemastine a prominent drug effect was seen. Thus, in dogs parenteral administration is a possible way of gaining therapeutic concentrations of clemastine.

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Résumé Les caractéristiques pharmacocinétiques de la clémastine ont été étudiées chez six chiens sains et les effets de la molécule sur l'inhibition de la formation de plaques ortiées après injection intradermique d'histamine ont été comparés. La clairance de la clémastine était élevée (moyenne: 2.1 L/h.kg) et le volume de distribution était important (13.4 L/kg). La demi-vie après administration iv était de 3.8 h et le taux de liaison aux protéines plasmatiques in vitro de 98 %. Après administration orale, la biodisponibilité était seulement de 3%. Après administration iv, la clémastine (0.1 mg kg^{-1}) a complètement inhibé la formation de plaque ortiée pendant 7 heures, alors que l'effet observé après administration orale (0.5 mg kg^{-1}) était mineur. Ces données montrent que la plupart des posologies proposées dans la littérature pour l'administration de clémastine chez le chien ne permettent pas d'obtenir un dosage systémique suffisant pour permettre un traitement efficace.

Resumen Se investigaron las propiedades farmacocinéticas de la clemastina en seis perros sanos y se comparó el efecto del fármaco registrando la inhibición de la formación de habones inducido por inoculaciones intradérmicas de histamina. La eliminación de clemastina fue elevada (media: 2.1 L/h.kg) y el volumen de distribución elevado (13.4 L/kg). La vida media después de la administración iv fue de 3.8 h y el nivel de unión con proteínas plasmáticas *in vitro* fue del 98%. Después de la administración oral, la biodisponibilidad fue solamente del 3%. Administrada iv, la clemastina (0.1 mg kg^{-1}) inhibía totalmente la formación del habón durante 7 horas, mientras que el efecto después de la administración oral (0.5 mg kg^{-1}) fue menor. Estos datos muestran que es probable que la mayoría de pautas de dosificación sugeridas en la bibliografía para la administración de clemastina a perros produzcan una exposición sistémica demasiado baja del fármaco para permitir una terapia efectiva.

Zusammenfassung Die pharmakinetischen Eigenschaften von Clemastin wurden bei sechs gesunden Hunden untersucht und mit der Wirkung des Medikamentes, das als Inhibition der Ausbildung von Quaddeln nach intradermaler Histamin-Injektion protokolliert wurde, verglichen. Die Clearance von Histamin war hoch (durchschnittlich 2,1l/h/kg) und sein Verteilungsvolumen groß (13,4 l/kg). Die Halbwertszeit nach i.v.-Gabe war 3,8 Stunden und die Plasmaproteinbindung in vitro lag bei 98%. Nach oraler Administration lag die Bioverfügbarkeit bei nur 3%. Nach intravenöser Gabe verhinderte Clemastin (0,1 mg/kg) die Quaddelbildung für 7 Stunden vollständig, während die Wirksamkeit nach oraler Administration (0,5 mg/kg) gering war. Die Daten zeigen, dass in der Literatur die meisten Dosierungsempfehlungen für die orale Gabe von Clemastin bei Hunden wahrscheinlich zu einer zu geringen systemischen Exposition des Medikamentes führen, um eine wirksame Therapie zu erlauben.