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Different Absorption Profiles of Deramciclane in Man and in Dog

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Abstract

We have studied the dog model for predicting the oral absorption of deramciclane, a novel anxiolytic compound, as a model acid-labile drug. The absorption profile of deramciclane was studied in man and beagle dogs after administration of conventional capsules and enteric coated tablets. Absorption in dogs pretreated with pentagastrin or saline was also studied after administration of conventional capsules. The in-vitro stability of deramciclane was determined over the pH range 1·2–6·0.

The rate of degradation of deramciclane increased ten-fold as the pH was reduced from 2·1 to 1·2 ($t_{\frac{1}{2}\beta}$ (elimination half-life) 9 h and 39 min, respectively). Deramciclane was stable at pH $\geq$ 3. The two formulations were bioequivalent in dogs and there were no significant differences between pharmacokinetic parameters measured for dogs pretreated with pentagastrin or saline. In man the mean relative bioavailability and C_{max} (peak plasma concentration) for the conventional capsules were approximately 75% and 83% of those for the enteric coated tablets ($P = 0.0004$ and $P = 0.0031$, respectively). This was probably because of degradation of deramciclane at lower pH of man's stomach compared with that of the dog. Pentagastrin was probably unsuccessful in reducing gastric pH and thus no change in absorption was observed.

It is concluded that the absorption of deramciclane, and possibly other acid-labile drugs, cannot be predicted by use of the dog model.

Laboratory animals are commonly used for preclinical pharmacokinetic studies and to screen new drug formulations before trials with man. Whereas small animals such as rodents are used to assess in-situ permeability and absorption mechanisms of drug molecules, larger animals such as dogs, cats, primates and pigs are used for screening new formulations. The dog is widely used for preclinical peroral absorption studies for human-scale dosage forms. The anatomy and dimensions of the gastrointestinal tract of the dog are essentially similar to those of man, the upper part of the tract in particular. The volumes of the stomach fundus are 1–1·6 L in man and approximately 1 L in dogs (Dressman & Yamada 1991). The lengths of the duodenum (25 cm in both species) and the jejunum (185–250 cm and 300 cm for dogs and man, respectively) are comparable (Dressman & Yamada 1991). The ileum and the colon are substantially shorter in dogs than in man (Kararli 1995) and the diameter of the small intestine is slightly different in the two species—2–2·5 and 3–4 cm for dogs and man, respectively (Dressman & Yamada 1991). In addition to the anatomical similarities, the dog is a good model because the animal is easy to handle and cooperative, the veins are accessible for blood sampling, and dogs are economical to use.

In-vivo pharmacokinetic data for oral drug-delivery systems from dog models are often not comparable with those from man (Aoyagi et al 1985) because of differences between the physiology of the gastrointestinal tracts and their metabolic capacities. The species' gastric pH are also different (Dressman & Yamada 1991; Kararli 1995). During fasting the mean gastric pH in man ranges from 1·1 to 1·5, although inter-individual variation can result in higher values (Lui et al 1986; Bendtsen et al 1987; Dressman et al 1990). The

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corresponding value in dogs is 1·5–4 (Lui et al 1986; Bendtsen et al 1987) and sometimes it is indistinguishable from duodenal pH (Dressman & Yamada 1991). The rate of secretion of gastric acid is much lower in dogs (0·1 mEq h^{-1}) than in man (2–5 mEq h^{-1}) resulting in a higher and broader range of pH values in dogs (Dressman & Yamada 1991). In contrast, under post-prandial conditions the gastric pH in dogs is lower (approx. 2) than in man (approx. 5). Consequently, the dissolution, solubilization and absorption of ionizable drugs by the two species can be different. The gastric transit time is an important variable for drugs which either are not absorbed from the stomach or which are unstable at low pH. Aoyagi et al (1992) have shown that the gastric residence times of tablets and granules are longer in man than in dog, differences that can influence drug absorption in dogs and result in misleading predictions of absorption in man. For example, different transit time and pH values in the stomach could result in different profiles for acid-labile compounds.

Deramciclane is a new non-benzodiazepine-like anxiolytic compound (Figure 1) with affinity for 5-HTergic 5-HT_{2A} and 5-HT_{2C} receptors, where it acts as an antagonist (Gacsályi et al 1997; Pälvimäki et al 1997). Deramciclane was selected as a model compound, because it has been shown to be completely absorbed from the gastrointestinal tract (Kanerva et al 1998; Lengyel et al 1998). The aim of this study was to reveal the effect of pH on the stability of deramciclane both in-vitro and in-vivo and to evaluate the usefulness of the dog for predicting the absorption of deramciclane in man.

Materials and Methods

Chemicals and formulations

Deramciclane fumarate was obtained from Egis Pharmaceuticals (Budapest, Hungary). Deramciclane fumarate 2·5 mg mL^{-1} injection solution was prepared by Orion Pharma (Espoo, Finland). Deramciclane fumarate 8·0 mg conventional hard gelatine capsules and 5·8 mg and 8·0 mg enteric coated tablets were manufactured by Egis Pharmaceuticals. The tablets were coated with methacrylic acid copolymer type C. A commercially available pentagastrin injection (Peptavlon 0·25 mg mL^{-1}; ICI, UK) was used. Analytical-grade chemicals were used in all analytical procedures.

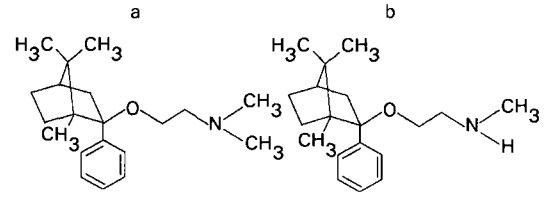

Figure 1. The molecular structures of deramciclane (a) and its metabolite *N*-desmethylderamciclane (b).

Animals

Six male laboratory-bred beagle dogs (Institute for Drug Research, Dunakeszi, Hungary), 15–19 months, 9·6–13·9 kg, were used to study the bioequivalence of deramciclane administered in conventional hard-gelatine capsules and in enteric coated tablets. All the animals were identified by an ear tattoo number made at weaning.

Two male and two female laboratory-bred beagle dogs (National Laboratory Animal Centre, University of Kuopio, Finland), 13 months, 8·5–12·5 kg, were used in the pentagastrin study.

Stability in-vitro

The stability of deramciclane was studied in-vitro over the pH range 1·2–6·0. Deramciclane (10 mg) was weighed into hydrochloric acid (HCl) solutions over the pH range 1·2–2·1 and in phosphate buffer solutions over the pH range 2·1–6·0. pH was verified by use of a PHM 22 Lab pH meter before adding deramciclane. The initial deramciclane concentration in the test solutions was 0·1 mg mL^{-1}. The test solutions were placed in a water bath at 37°C, and a zero-time sample (2 mL) was taken immediately. Thereafter the samples were taken after 25, 50, 75, 100 and 125 min. Deramciclane concentrations were determined by HPLC without sample preparation.

Bioequivalence in dog

The bioequivalence of deramciclane fumarate conventional capsules and enteric coated tablets at a dose of 0·5 mg kg^{-1} were studied in fasting dogs. A non-randomized cross-over study design with a 16-day wash-out period was used. The capsule formulation was administered first. Deramciclane fumarate was weighed into empty hard-gelatine capsules without excipients according to the body weight of the dog measured on the previous day. The enteric coated tablets contained a total dose of deramciclane fumarate of 5·8 mg, which resulted in a relative dose of $0·5 \pm 0·06$ mg kg^{-1}.

Pentagastrin treatment in dogs

To reduce the gastric pH each dog was pretreated with pentagastrin. A 6 μg kg^{-1} dose of pentagastrin or an equivalent volume of physiological saline was given as an intramuscular bolus 20 min before administration of deramciclane fumarate. A 3 mg kg^{-1} oral dose of deramciclane fumarate was

given in a hard-gelatine capsule (no. 0) without excipients. A 3 mg kg^{-1} intravenous dose was administered without pretreatment to evaluate the absolute bioavailability. A three-way cross-over design with a one-week wash-out period was used. Dosing was performed in the order intravenous bolus, reference oral with saline pretreatment and oral dosing with pentagastrin pretreatment.

Blood sampling

Blood samples were taken from the jugular vein into tubes containing Na_2EDTA. Blood samples were centrifuged and plasma was stored at −20°C or below until analysed. During treatment with 0·5 mg kg^{-1} as a conventional capsule or as enteric coated tablets blood samples were drawn before dosing and up to 36 and 48 h, respectively. In the pentagastrin study the blood samples were taken up to 72 h after oral and intravenous administration.

Animal studies were performed according to national and European laws and regulations for the use of laboratory animals for research.

Bioequivalence in man

An open cross-over design of two treatment periods separated by a two-week wash-out period was used to compare 8 mg deramciclane fumarate conventional capsule and 8 mg deramciclane fumarate in an enteric coated tablet. The study subjects were randomly allocated to either of the two treatment sequences by use of randomized blocks. The subjects received the study number and treatment sequence according to the randomization list as they entered the study. The study was performed on 16 healthy Caucasian male volunteer recruits, 26·3 ± 3·6 years, 77·6 ± 7·4 kg, body mass index 22·3 ± 1·7 cm kg^{-2}.

Blood samples were taken via a cannula from the antecubital vein before drug intake (zero sample) and then up to 72 h. Deramciclane was administered to subjects in a fasting state which was maintained until 4 h post-treatment.

The blood samples were collected into 10-mL Vacutainer glass tubes containing Na_2EDTA. The samples were centrifuged immediately at 3000 rev min^{-1} for 10 min at +4°C. The plasma from each sample was immediately pipetted into two plastic tubes and stored below −20°C until analysed.

This study was performed according to the Good Clinical Practice Guidelines of the European Community and followed the recommendations for biomedical research involving man (current revision of the Declaration of Helsinki of the World Medical Assembly). The study protocol, the subject information text and the consent form were submitted to the ethics committee for approval. Approval was obtained before initiation of the study.

Chemical analysis

In the in-vitro acid stability study deramciclane concentrations were determined by HPLC (HP1050, Hewlett-Packard) with a μBondapak C18 column (300 mm × 3·9 mm, 10 μm particles) and a UV-detector operated at 254 nm. The mobile phase was acetonitrile–methanol–0·01 M KH_2PO_4, 10 : 70 : 20 (v/v). The flow rate was 1·0 mL min^{-1}. The retention time of deramciclane was 6·8 min. Only deramciclane was analysed. The degradation products were not identified, because no reference standards were available.

Deramciclane and its active metabolite *N*-desmethylderamciclane were determined in dog plasma by gas chromatography with a nitrogen-sensitive detector. The methods used have been described in detail elsewhere (Nemes et al 1996; Klebovich et al 1997). For the both analytes in the pentagastrin study the limits of quantitation had an inter-day variation of 2·5 ng mL^{-1} with relative standard deviations of 16·7 and 12·7%, respectively. The limit of quantitation for deramciclane in the bioequivalence study was 0·5 ng mL^{-1} with a relative standard deviation of 10·6%.

The plasma samples from man were analysed by liquid chromatography-tandem mass spectrometry. The analytes were extracted from plasma with diethyl ether after addition of deuterium-labelled deramciclane ([$^2H_5$]deramciclane) as internal standard. The liquid chromatographic system consisted of a HP Model 1090 Series II HPLC pump and an autosampler (Hewlett-Packard, Avondale, CA) and an Asahipak polymeric-phase column (125 mm × 4 mm i.d., 5 μm particles, Hewlett-Packard). The mobile phase was methanol–acetonitrile–2 mM ammonium acetate, 70 : 5 : 25 (v/v), pH 5·0. The flow-rate was 1·0 mL min^{-1}. The column effluent was directed to a Sciex heated nebulizer probe (Tornhill, Ontario, Canada). A Sciex API III triple-quadrupole mass spectrometer equipped with a standard atmospheric-pressure ionization source was used to sample ions produced from the heated nebulizer interface. The discharge-needle current was set at a voltage of 5000 V. The nebulizer-gas (air) pressure was 75 psi and the auxiliary gas flow-rate 2·0 L min^{-1}. The nitrogen curtain gas was adjusted to a flow-rate of 1·1 L min^{-1}. The interface heater was set at 57°C and the orifice plate voltage was 35 V. Argon (99·9999%) was used as collision gas. The first quadrupole filter of the mass spectrometer, Q1, was set to pass the protonated molecular ions of

N-desmethylderamciclane, deramciclane and the internal standard, at m/z 288, 302 and 307 for collision-induced fragmentation in Q2 (ion-energy 10 eV); the respective product ions, at m/z 213, 213 and 218 were then monitored with Q3. The dwell time was 200 ms and the pause time 50 ms. The quantitation limit was 100 pg mL^{-1} for deramciclane and *N*-desmethylderamciclane; the relative standard deviations were 3·5% and 6·0%, respectively.

Pharmacokinetic calculations

The pharmacokinetic parameters were calculated by use of the Siphar/Win 1·2b program (Simed Biostatistics and Data Processing, Creteil, France). In the dog studies plasma deramciclane concentration data were fitted to a two-compartment model. The pharmacokinetic parameters of *N*-desmethylderamciclane and deramciclane in plasma from man were calculated model-independently.

The areas under the concentration–time curves (AUC) for deramciclane and *N*-desmethylderamciclane were calculated by use of the linear trapezoidal rule. The area beyond $C_{t\ last}$ (the last concentration measured) was extrapolated to infinity by dividing $C_{t\ last}$ by the slope of the elimination phase (λ_z). The mean residence time (MRT) was calculated from:

$$MRT = AUMC/AUC_{0-\infty} \quad (1)$$

The absolute bioavailability (F) of deramciclane in the dog was calculated by comparing $AUC_{0-\infty}$ values after oral and intravenous administration. The peak plasma concentration (C_{max}) of deramciclane and the time to reach it (T_{max}) were read directly from the observed individual plasma concentration–time data. Lag-time was calculated by the Wagner-Nelson method (Rowland & Tozer 1995). Total clearance (CL_{tot}) of deramciclane after intravenous administration was calculated from:

$$CL_{tot} = D/AUC_{0-\infty} \quad (2)$$

where D is the dose administered. The volume of distribution V_z was calculated from:

$$V_z = CL_{tot}/\lambda_z. \quad (3)$$

Statistical analysis

The pharmacokinetic parameters are presented as means ± s.d. A non-parametric method, the Wilcoxon signed rank test, was used for statistical comparisons of all pharmacokinetic parameters. Significance level was set at $P < 0.05$. In addition, 90 and 95% confidence intervals were calculated for similarity of AUC values, C_{max} and their logarithmic transformations for the ratio between the means of the two formulations in man to evaluate the bioequivalence.

Results and Discussion

This study has revealed the acid-labile nature of deramciclane, in particular over the pH range 1·2–2·1 (Figure 2a). Deramciclane was quite stable at pH 2·1 (half-life, $t_{\frac{1}{2}} = 9$ h) and there was practically no degradation at pH ≥ 3. At pH 1·2 the compound degraded rapidly ($t_{\frac{1}{2}} \approx 39$ min). Because the degradation rate constant increased approximately tenfold as pH was reduced from 2·1 to 1·2 (Figure 2b), degradation of deramciclane was expected to be dependent on changes in stomach pH, which could interfere with the bioavailability of the compound in-vivo.

The pharmacokinetic parameters of deramciclane for the two formulations in dog are shown in Table 1. There were no statistical differences between the $AUC_{0-\infty}$ values for the conventional hard-

Table 1. Pharmacokinetic parameters for deramciclane in dog after single intravenous or oral administrations of 3 mg kg^{-1} deramciclane fumarate with oral saline or pentagastrin pretreatment, and single oral administration of 0·5 mg kg^{-1} as a conventional hard-gelatine capsule or as an enteric coated tablet.

Parameter	3 mg kg^{-1} intravenous	3 mg kg^{-1} oral + saline	3 mg kg^{-1} oral + pentagastrin	0·5 mg kg^{-1} capsule	0·5 mg kg^{-1} enterotablet
C_{max} (ng mL^{-1})	248 ± 28·6	91·8 ± 40	86·3 ± 34·3	7·29 ± 4·42	7·22 ± 5·23
T_{max} (h)	0·23 ± 0·20	1·9 ± 0·85	1·5 ± 0·41	2·1 ± 0·41	3·3 ± 0·52
$AUC_{0-\infty}$ (ng h mL^{-1})	1555 ± 149	823·6 ± 203·9	720·1 ± 159·9	60·50 ± 39·79	51·97 ± 35·71
$t_{\frac{1}{2}\beta}$ (h)	9·9 ± 2·4	8·0 ± 3·9	11·5 ± 5·2	9·3 ± 1·2	7·44 ± 1·5
MRT (h)	11·0 ± 1·11	17·2 ± 12·7	13·1 ± 5·31	10·9 ± 1·63	10·0 ± 0·551
F (%)	NA	53 ± 11	46 ± 8·5	NA	NA
CL_{tot} (h^{-1})	19·7 ± 1·46	NA	NA	NA	NA
V_z (L)	282 ± 75·5	NA	NA	NA	NA

C_{max}, maximum concentration; T_{max}, time of maximum concentration; $AUC_{0-\infty}$, area under the plot of plasma concentration against time; $t_{\frac{1}{2}\beta}$, elimination half-life; MRT, mean residence time; F, bioavailability; CL_{tot}, total clearance; V_z, volume of distribution. NA, not applicable.

gelatine capsule and the enteric coated tablet. The plots of plasma-concentration against time for the formulations were similar (Figure 3) suggesting no degradation of deramciclane by gastric acid. This might be because of reduced secretion of hydrochloric acid during fasting, resulting in higher pH (Dressman & Yamada 1991) and so the pH in the dogs' stomachs could have been > 2·1, resulting in no degradation. Lengyel et al (1998) reported that [^{14}C]deramciclane did not disintegrate in the isolated dog stomach at pH 2·0 ± 0·1. This is in accordance with our results and suggest that the critical pH is < 2.

In this study pentagastrin pretreatment did not significantly affect $AUC_{0-\infty}$ values or absolute bioavailability of deramciclane (Figure 4, Table 1). It is possible that deramciclane was administered too early after pentagastrin injection and, therefore, the gastric pH was not low enough for deramciclane degradation. Unfortunately, stomach pH was not monitored in this study. Alternatively, the higher gastric emptying rate in dog than in man (Aoyagi et al 1992) might have reduced the exposure of deramciclane to an acidic environment.

The absorption of deramciclane given in conventional capsules and in enteric coated tablets was studied in healthy male volunteers to determine whether the acid-labile nature of deramciclane had any relevance in man. The pharmacokinetic parameters are presented in Table 2. The plots of plasma concentration against time in man were different for the different formulations (Figure 5a, b). After intake of the capsule deramciclane could be detected in plasma sampled as early as 20 min post-dosing whereas for the enteric tablet the mean lag-time was 2·7 h. The longer lag-time in man (Figures 3 and 4) could be explained by the higher gastric emptying rate of solid particles in dogs (Aoyagi et al 1992). The mean C_{max} for the enteric coated tablet was significantly higher than for the capsule ($P = 0{\cdot}0031$) and this peak was reached much earlier for the capsule ($P = 0{\cdot}0001$). The MRT and $t_{\frac{1}{2}\beta}$ (elimination half-life)

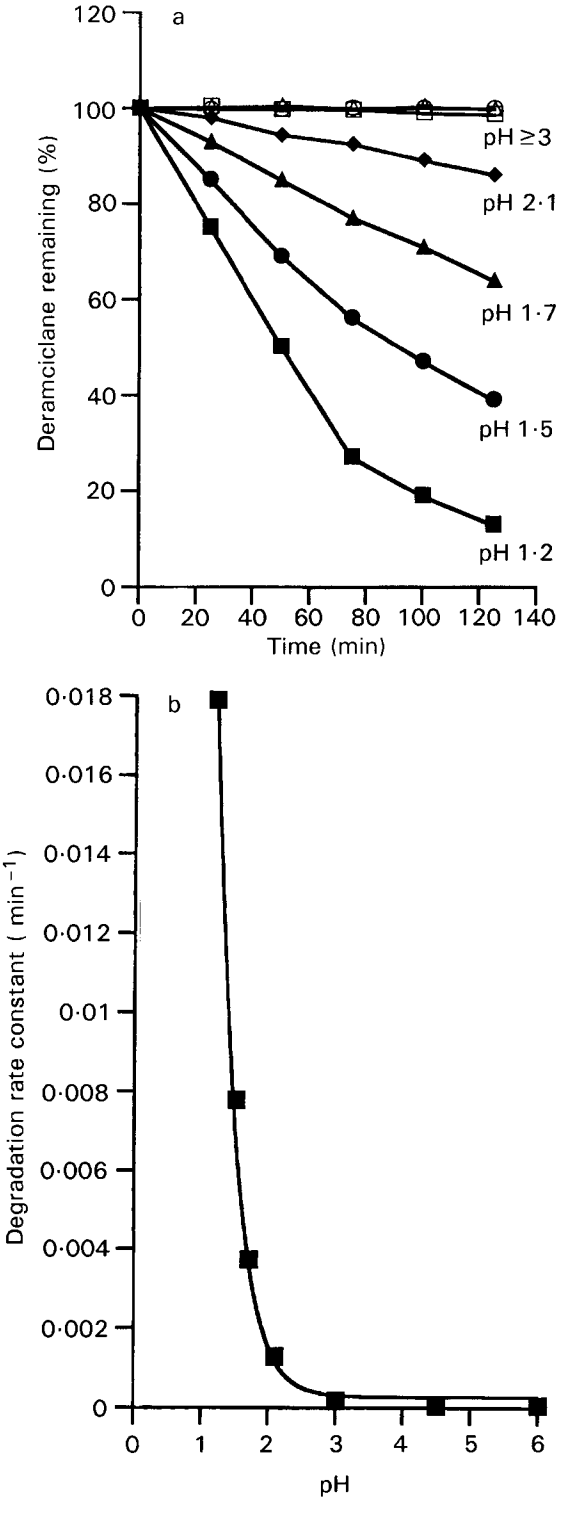

Figure 2. The in-vitro degradation of deramciclane in the pH range 1·2–6·0 (a) and the first-order rate of degradation of deramciclane as a function of pH (b).

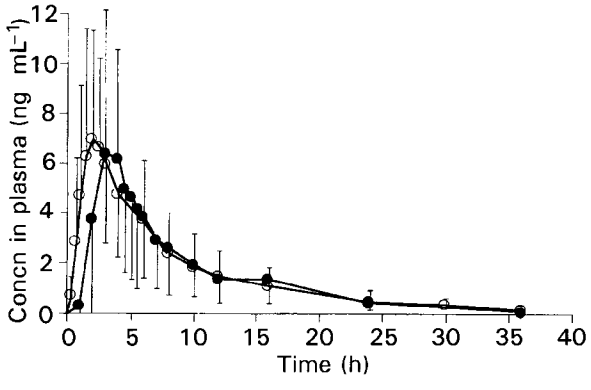

Figure 3. Mean (± s.d.) plasma concentration–time curves for deramciclane after a 0·5 mg kg^{-1} single oral dose of deramciclane fumarate given as a conventional hard-gelatine capsule (○) or as an enteric coated tablet (●) to six beagle dogs.

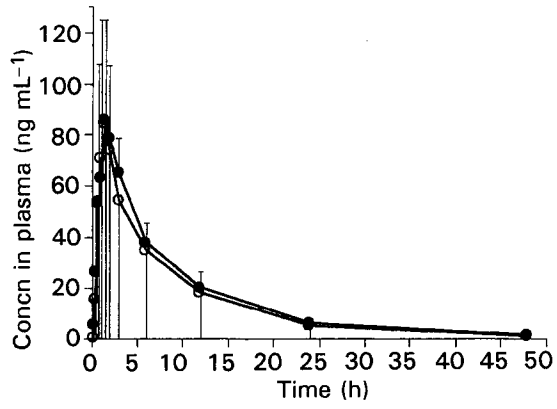

Figure 4. Mean (± s.d.) plasma concentration–time curves for deramciclane in four beagle dogs after pentagastrin (○) or saline (●) pretreatment and then a single oral dose of 3 mg kg^{-1} of deramciclane fumarate.

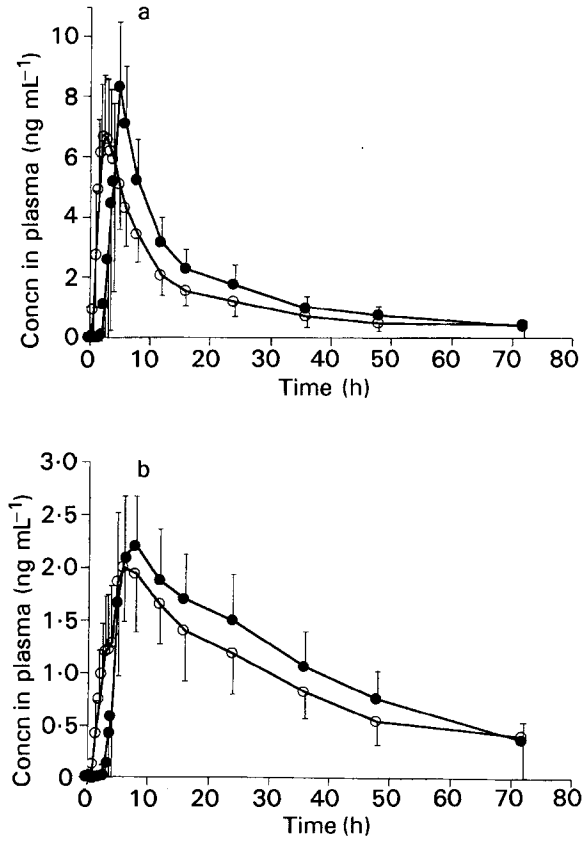

Figure 5. Mean (± s.d.) plasma concentration–time curves for deramciclane (a) and *N*-desmethylderamciclane (b) after an 8·0-mg single oral dose of deramciclane fumarate given as a conventional hard gelatine capsule (○) or as an enteric coated tablet (●) to 16 healthy male volunteers.

were significantly longer for the enteric coated tablets than for conventional capsules ($P = 0.0013$ and $P = 0.034$, respectively). The greater MRT values of the tablets reflect delayed onset of absorption rather than changes in elimination. In man the relative bioavailability of the capsule was approximately 75% that of the enteric coated tablet ($P = 0.0004$). The 90% confidence intervals of $AUC_{0-\infty}$ and C_{max} for deramciclane are presented in Table 2. The upper limits of the confidence intervals for both parameters exceeded the criteria for bioequivalence, indicating that the two formulations were not bioequivalent.

As for the parent compound, the formation of *N*-desmethylderamciclane in man was significantly less for the capsule ($P = 0.0006$) and the AUC values, as evaluated by means of 90% confidence intervals (Table 2), were not bioequivalent. However, differences between values of C_{max} and T_{max} for *N*-desmethylderamciclane after administration of capsule and tablet were not significant. The low stomach pH in man might have caused degradation of deramciclane and, thus, the total amount of deramciclane available for absorption in the gastrointestinal tract might have been less after administration of the conventional capsule. Consequently, under fasting conditions formation of

Table 2. Pharmacokinetic parameters for deramciclane and its main metabolite *N*-desmethylderamciclane for 16 healthy Caucasian male volunteers receiving 8·0 mg deramciclane fumarate as a conventional hard-gelatine capsule and as an enteric coated tablet.

Parameter	Capsule	Tablet	90% confidence interval
Deramciclane			
C_{max} (ng mL^{-1})	7·18 ± 19·3	8·65 ± 24·4	1·13; 1·27; $P = 0.0031$
T_{max} (h)	2·6 ± 0·67	4·8 ± 0·66	$P = 0.0001$
$AUC_{0-\infty}$ (ng h mL^{-1})	102·3 ± 35·8	134·5 ± 41·7	1·24; 1·39; $P = 0.0004$
$t_{\frac{1}{2}\beta}$ (h)	23·9 ± 7·5	28·9 ± 8·3	$P = 0.034$
MRT (h)	25·8 ± 7·2	32·8 ± 7·1	$P = 0.0013$
N-Desmethylderamciclane			
C_{max} (ng mL^{-1})	2·13 ± 0·565	2·32 ± 0·537	1·01; 1·16; NS
T_{max} (h)	6·4 ± 1·9	7·2 ± 1·7	NS
$AUC_{0-\infty}$ (ng h mL^{-1})	62·6 ± 18·8	76·3 ± 20·6	1·14; 1·30; $P = 0.0006$
$t_{\frac{1}{2}\beta}$ (h)	NA	NA	NA
MRT (h)	NA	NA	NA

C_{max}, maximum concentration; T_{max}, time of maximum concentration; $AUC_{0-\infty}$, area under the plot of plasma concentration against time; $t_{\frac{1}{2}\beta}$, elimination half-life; MRT, mean residence time. NA, not applicable. NS, not significant.

N-desmethylderamciclane was significantly less after administration of the conventional capsule than after administration of the enteric coated tablet.

Extensive degradation of deramciclane was observed in in-vitro stability experiments; at pH 1·2 only approximately 13% of the initial concentration was seen after 125 min (Figure 2a). Degradation was strongly pH-dependent, and no degradation occurred at pH 3 or above. In man the mean gastric pH in the fasting state is 1·1–1·5, although inter-individual variation might lead to higher values (Lui et al 1986; Bendtsen et al 1987; Dressman et al 1990). By taking into account the retention times (20–60 min) of granules in the stomach (Clements et al 1978; Digenis et al 1990) and the rates of degradation of deramciclane at pH 1·1–1·5, a substantial fraction of the drug might degrade. Therefore, the smaller relative bioavailability of deramciclane from a conventional capsule was probably because of the disintegration of the drug. This was in contrast to results from dogs (no difference between the formulations). These species differences might be because of different stomach pH, but it must be emphasized that we did not measure stomach pH either in dogs or man. It is concluded that absorption profiles of deramciclane, and possibly other acid-labile drugs, in dogs cannot be used to predict absorption in man. This is a limitation of the dog model and should be taken into account in absorption studies with acid-labile drugs.

References

Aoyagi, N., Ogata, H., Kaniwa, N., Ejima, A., Nakata, H., Tsutsumi, J., Fujita, T., Amada, I. (1985) Bioavailability of indomethacin capsules in humans (III): correlation with bioavailability in beagle dogs. Int. J. Clin. Pharmacol. Ther. Toxicol. 32: 578–584

Aoyagi, N., Ogata, H., Kaniwa, N., Uchiyama, M., Yasuda, Y., Tanioka, Y. (1992) Gastric emptying of tablets and granules in humans, dogs, pigs, and stomach-emptying-controlled rabbits. J. Pharm. Sci. 81: 1170–1174

Bendtsen, F., Rosenkilden-Gram, B., Tage-Jensen, U., Ovesen, L., Rune, S. (1987) Duodenal bulb acidity in patients with duodenal ulcer. Gastroenterology 93: 1263–1269

Clements, J., Heading, R., Nimmo, W., Prescott, L. (1978) Kinetics of acetaminophen absorption and gastric emptying in man. Clin. Pharmacol. Ther. 24: 420–431

Digenis, G., Sandefer, E., Parr, A., Beihn, R., McClain, C., Scheinthal, B., Ghebre-Sellassie, I., Iyer, U., Nesbitt, R., Randinitis, E. (1990) Gastrointestinal behaviour of orally administered radiolabelled erythromycin pellets in man as determined by gamma scintigraphy. J. Clin. Pharmacol. 30: 621–631

Dressman, J. B., Yamada, K. (1991) Animal models for oral drug absorption. In: Welling, P., Tse, F. L. (eds) Pharmaceutical Bioequivalence. Dekker, New York, pp 235–266

Dressman, J. B., Berardi, R., Dermentzoglou, L., Russell, T. L., Schmaltz, S. P., Barnett, J. L., Jarvenpaa, K. M. (1990) Upper gastrointestinal (GI) pH in young, healthy men and women. Pharm. Res. 7: 756–761

Gacsályi, I., Schmidt, E., Gyertyán, I., Vasar, E., Lang, A., Haapalinna, A., Fekete, M., Hietala, J., Syvalahti, E., Tuomainen, P., Männistö, P. T. (1997) Receptor binding profile and anxiolytic activity of deramciclane (EGIS-3886) in animal models. Drug Dev. Res. 40: 333–348

Kanerva, H., Huuskonen, H., Alhonen-Raatesalmi, A., Nevalainen, T., Urtti, A. (1998) Pharmacokinetics of deramciclane in dogs after single oral and intravenous dosing and multiple oral dosing. Biopharm. Drug Dispos. In press

Kararli, T. T. (1995) Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharm. Drug. Dispos. 16: 351–380

Klebovich, I., Leibinger, J., Abermann, M., Grezál, G. Y. (1997) A sensitive, validated gas chromatographic bioanalytical method by nitrogen selective detection of deramciclane in dog plasma. Pharm. Sci. 3: 497–501

Lengyel, J., Bolehovsky, A., Klebovich, I., Aberman, M., Magyar, K. (1998) Absorption of deramciclane in rats, dogs and rabbits. Arzneim. Forsch. 48: 455–460

Lui, C. Y., Amidon, G. L., Berardi, R. R., Fleisher, D., Youngberg, C., Dressman, J. B. (1986) Comparison of gastrointestinal pH in dogs and humans: implications on the use of the beagle dog as a model for oral absorption in humans. J. Pharm. Sci. 75: 271–274

Nemes, K. B., Abermann, M., Bojti, E., Klebovich, I. (1996) A highly sensitive GC method for the determination of deramciclane and its *N*-desmethyl metabolite in rat and dog plasma. In: Reid, E., Hill, H. M., Wilson, I. D. (eds) Biofluid Assay for Peptide-related and Other Drugs. Methodological Surveys in Bioanalysis of Drugs, 24. The Royal Society of Chemistry, Cambridge, pp 103–104

Pälvimäki, E.-P., Majasuo, H., Kuoppamäki, M., Männistö, P. T., Syvälahti, E., Hietala, J. (1998) Deramciclane, a putative anxiolytic drug, is a serotonin 5-HT_{2C} receptor inverse agonist but fails to induce 5-HT_{2C} receptor down-regulation when administered chronically. Psychopharmacology. 136: 99–104

Rowland, M., Tozer, T. N. (1995) Clinical Pharmacokinetics: Concepts and Applications. 3rd edn, Lea & Febiger, Philadelphia, pp 478–484