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Excretion of the dipeptidyl peptidase-4 inhibitor linagliptin in rats is primarily by biliary excretion and P-gp-mediated efflux

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ABSTRACT

Linagliptin is a selective, competitive dipeptidyl peptidase-4 (DPP-4) inhibitor, recently approved in the USA, Japan and Europe for the treatment of type 2 diabetes. It has non-linear pharmacokinetics and, unlike other DPP-4 inhibitors, a largely non-renal excretion route. It was hypothesised that P-glycoprotein (P-gp)-mediated intestinal transport could influence linagliptin bioavailability, and might contribute to its elimination. Two studies evaluated the role of P-gp-mediated transport in the bioavailability and intestinal secretion of linagliptin in rats. In the bioavailability study, male Wistar rats received single oral doses of linagliptin, 1 or 15 mg/kg, plus either the P-gp inhibitor, zosuquidar trihydrochloride, or vehicle. For the intestinal secretion study, rats underwent bile duct cannulation, and urine, faeces, and bile were collected. At the end of the study, gut content was sampled. Inhibition of intestinal P-gp increased the bioavailability of orally administered linagliptin, indicating that this transport system plays a role in limiting the uptake of linagliptin from the intestine. This effect was dependent on linagliptin dose, and could play a role in its non-linear pharmacokinetics after oral dosing. Systemically available linagliptin was mainly excreted unchanged via bile (49% of i.v. dose), but some (12%) was also excreted directly into the gut independently of biliary excretion. Thus, direct excretion of linagliptin into the gut may be an alternative excretion route in the presence of liver and renal impairment. The primarily non-renal route of excretion is likely to be of benefit to patients with type 2 diabetes, who have a high prevalence of renal insufficiency.

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a new class of oral agents for controlling blood glucose in patients with type 2 diabetes (Del Prato et al., 2011; Scheen, 2010; Taskinen et al., 2011). They act by enhancing the effect of incretins, particularly glucagon-like peptide-1 and glucose-dependent insulinotropic peptides by inhibiting their enzymatic degradation. These intestinal peptides are secreted in response to food intake and play an important role in controlling postprandial glucose levels by enhancing glucose-dependent insulin release and reducing glucagon secretion (Bohannon, 2009; Deacon and Holst, 2010; Scheen, 2010). This approach to reducing hyperglycaemia in type 2 diabetes is potentially superior to conventional insulinotropic agents that often act independently of blood glucose levels. As a result, DPP-4 inhibitors are less likely to cause hypoglycaemia than insulin, sulphonylureas, or metaglinides, and do not produce weight gain that can be associated with insulin, sulphonylurea, or thiazolidinedione therapy (Hüttner et al., 2008).

Linagliptin is a xanthine-based, selective, competitive DPP-4 inhibitor which has recently been approved in the USA, Japan and Europe for the treatment of type 2 diabetes. It has an unusual pharmacokinetic profile within the DPP-4 inhibitor class, both in relation to its binding to plasma proteins and its route of elimination, as described below (Deacon and Holst, 2010; Fuchs et al., 2009b; Heise et al., 2009; Thomas et al., 2008). In contrast to other DPP-4 inhibitors (sitagliptin, vildagliptin, and saxagliptin), linagliptin binds extensively to plasma proteins in a concentration-dependent manner (Fuchs et al., 2009b). The high-affinity binding of linagliptin to DPP-4 in plasma and tissues produces a long terminal half-life ($t_{1/2}$) and a non-linear pharmacokinetic profile, which has been demonstrated in both animal models (Fuchs et al., 2009a,b; Retlich et al., 2009) and humans (Heise et al., 2009). Non-linear pharmacokinetics can result from several factors and for linagliptin are related, at least in part, to a concentration-dependent change in plasma protein binding, where the binding of linagliptin to DPP-4 is characterised by high affinity but low capacity. Thus, when binding to DPP-4 is saturated, the free fraction of linagliptin rises, resulting in an increase in drug elimination (Fuchs et al., 2009b). In addition, high-affinity, saturable binding to DPP-4 in tissues was observed (Fuchs et al., 2009a). These features of linagliptin account for some of the observed non-linear pharmacokinetic profile

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of the drug, including the rapid attainment of steady state and limited drug accumulation, as well as a long-lasting effect of the drug on DPP-4 inhibition (Fuchs et al., 2009a; Heise et al., 2009). Linagliptin is predominantly eliminated unchanged after oral or i.v. administration in rats and in humans (Blech et al., 2010). Linagliptin has a largely non-renal route of excretion (5% excreted renally), with the majority being excreted in the faeces, although the drug undergoes some biotransformation, with the main metabolite being a pharmacologically inactive hydroxypiperidinyl derivative of the drug, CD 1790 (Blech et al., 2010).

Linagliptin is a substrate for P-glycoprotein (P-gp) (Boehringer Ingelheim, Data on File). P-gp-mediated intestinal transport is a significant component of the barrier to the efficient intestinal absorption of many drugs; it has been hypothesised as having a role in limiting the bioavailability of linagliptin, and might also play a role in its non-linear pharmacokinetics after oral dosing. The P-gp transport system is located in the intestinal epithelium, where it limits the bioavailability of many drugs by actively transporting them into the gut lumen (Stephens et al., 2002). To further explore the role of P-gp in the absorption of linagliptin, a rat study was performed to evaluate the effect of intestinal P-gp inhibition by zosuquidar trihydrochloride, a selective P-gp inhibitor (Kwon et al., 2004; Starling et al., 1997; Stephens et al., 2002), on the oral bioavailability of linagliptin.

In addition to the pharmacokinetic features mentioned above, another important difference between linagliptin and other DPP-4 inhibitors is its route of elimination. The main elimination route of the DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin, and alogliptin is via the kidney, and dose adjustment in patients with renal impairment (e.g. diabetic nephropathy or renal failure) may therefore be necessary (Scheen, 2010). In contrast, only a low fraction of linagliptin is eliminated via the kidneys. In healthy volunteers it is largely excreted in the faeces, with 85% of a 10 mg oral dose and 58% of a 5-mg i.v. dose being excreted by this route, whereas renal excretion accounted for only 5% of the oral dose and 31% of the i.v. dose (Blech et al., 2010). Similarly, less than 1% of an oral dose of linagliptin 5 mg was excreted unchanged in the urine in healthy individuals (Hüttner et al., 2008). To further understand the mechanism of the non-renal excretion of linagliptin, experiments to investigate its biliary excretion and the role of the intestinal P-gp-mediated secretion were conducted in rats. The objectives of the first study were to investigate the influence of intestinal P-gp inhibition on the oral bioavailability of linagliptin and on the pharmacokinetics of a high oral dose of linagliptin. The purpose of the second study was to investigate the biliary excretion of linagliptin over an extended period of time following a single oral dose, and to evaluate the effect of elimination of linagliptin by direct secretion into the gut.

2. Methods

2.1. Animals

Male Wistar rats, of the strain Crl:WI(Han) were supplied by Charles River (Sulzfeld, Germany).

2.2. In vivo experiments

2.2.1. Evaluation of oral bioavailability of linagliptin with and without P-gp inhibition

For plasma sampling, the animals were housed in groups of two in Macrolon cages, under constant environmental conditions (with a cycle of 12 h light/12 h dark). Rats were fasted for 12 h before, and 2 h after, drug administration; tap water was freely available throughout the studies. The experiments involved four treatment groups: single oral doses of linagliptin, 1 or 15 mg/kg (2.12 or 31.8 μmol/kg), were administered to the rats. For each dose, the rats received either oral zosuquidar (zosuquidar trihydrochloride, synthesized by Boehringer Ingelheim, Germany), 2.64 mg/kg (5 μmol/kg), or vehicle, each administered 5 min before linagliptin dosing. This dose was selected based on the previous observation that oral administration of 5 μmol/kg (2.64 mg/kg) zosuquidar, 5 min before administration of various probe compounds resulted in specific inhibition of P-gp in the gut without affecting P-gp-mediated biliary efflux of i.v. administered P-gp substrates or the pharmacokinetics of orally administered CYP3A substrates in the rat (unpublished data).

The oral linagliptin was administered as 0.2 and 3 mg/mL in tap water. Zosuquidar trihydrochloride, 1 mM, in 5% glucose solution, was orally administered. Approximately 0.3 mL of blood was withdrawn from the sublingual vein, under isofluorane anaesthesia, at the following time points after drug administration: 0.25, 0.5 h, then hourly between 1 and 8 h, then at 24, 48, and 72 h.

2.2.2. Biliary and intestinal excretion

For the intestinal secretion studies, a single i.v. dose of 1 mg/kg of [^{14}C]linagliptin was injected as a bolus via the tail vein in bile duct cannulated rats. For implantation of the bile cannula, animals were anaesthetized with two-parts Ketamin (10%) (Intervet GmbH, Germany) plus one-part Rompun® (Bayer Health Care, Germany), administered intraperitoneally (1 mL/kg). The bile duct was cannulated with a catheter drawn under the skin from the neck region to the abdominal cavity. The catheter was fixed to the neck with a septum. After surgery, the rats were kept in specially designed cages that allowed free movement (Raturn®, BASi, West Lafayette, IN, USA) and were designed for separate collection of urine, faeces, and bile. Rats were given food and water *ad libitum*.

Faeces (0–8 h, 0–24 h) and urine (0–8 h, 8–24 h) were collected, in addition to cage washings (every 24 h). Bile was also collected hourly between 0 and 8 h after dosing, and overnight (8–24 h after dosing). Urine, bile, and faeces samples were cooled to 4–8 °C, and then frozen to about −20 °C.

At the end of the experiments (24 h after dosing), the animals were sacrificed by an overdose of inhaled isoflurane, and the gut content was sampled.

2.3. Bioanalysis of samples

Plasma for the pharmacokinetic analyses was extracted from blood samples and stored at −20 °C. The formation of the main metabolite by oxidative deamination is highly stereo selective, leading to an *S*-enantiomeric entity (code CD 1790). For the quantification, the corresponding racemic mixture (code CD 1750) was used as the reference standard.

A high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC–MS/MS) method for the quantification of linagliptin and its metabolite CD 1750 in rat plasma based on a fully validated (U.S. Department of Health and Human Services Food and Drug Administration, 2001) assay with a more sensitive lower limit of quantification was used. Samples were cleaned-up by solid phase extraction in the 96-well plate format on a Varian SPEC MP3 (C8/SCX) extraction plate. Linagliptin and CD 1790 were analyzed using [$^{13}C_3$]linagliptin and [$^{13}C_3$]CD 1750 as internal standards. Chromatography was conducted using an analytical reverse-phase column with gradient elution. Plasma levels of linagliptin and CD 1790 were quantified by HPLC-MS/MS using electrospray ionization in the positive ion mode with a lower limit of quantification of 0.50 nmol/L for linagliptin and 0.25 nmol/L for CD 1790 (referring to undiluted samples).

Radioactivity in urine, faecal and bile samples, and gut content were quantified by liquid scintillation counting.

2.4. Data analysis

2.4.1. Bioavailability analysis

Plasma concentration–time data for linagliptin and its metabolite were analyzed with the programme ToxKin 3 (Entimo, Berlin, Germany), and descriptive statistics were calculated. For linagliptin and its metabolite, peak plasma concentrations (C_{max}) and time to reach maximum plasma level (T_{max}) were calculated, and the area under the plasma level–time curve, from 0 to 72 h (AUC_{0-72h}) estimated using the linear trapezoid rule. An extrapolated AUC, from time 0 to infinity ($AUC_{0-\infty}$), was also calculated. Half-life was calculated as $t_{1/2} = \ln 2/\lambda_z$, with the terminal elimination rate constant λ_z as the negative slope of the logarithmic linear regression line using the last data points. For the pharmacokinetic evaluation, it was assumed that 1 kg of blood equals 1 L and, therefore, that [nmol/kg] equals [nmol/L] of blood or plasma.

2.4.2. Intestinal excretion analysis

Data obtained from liquid scintillation counting were transferred to the data and acquisition handling system, DEBRA (LabLogic, Sheffield, UK), which was used to calculate statistics for radioactivity data and produce summary tables. Radioactivity concentrations were determined based on sample weights (g) and specific activity (MBq/μmol).

3. Results

Data were obtained from four animals in each of the four treatment groups. Both individual and mean plasma concentrations of linagliptin showed relevant increases in C_{max} and AUC_{0-72h} for both linagliptin doses in animals that had been pre-treated with zosuquidar trihydrochloride, compared with those that were not, at both linagliptin doses (Fig. 1). Moreover, data in Table 1 show that dose-normalised C_{max} increased by a factor of approximately 7.4, and dose-normalised AUC_{0-72h} by approximately 1.5-times between linagliptin doses of 1 and 15 mg/kg.

Pre-treatment with zosuquidar trihydrochloride resulted in a substantial increase in C_{max} and AUC_{0-72h}, which was most marked at the lower linagliptin dose: C_{max} increased by factors of approximately 14 and 1.4 with oral linagliptin doses of 1 and 15 mg/kg, respectively. Corresponding increases in AUC_{0-72h} were 2.1- and 1.4-fold, respectively.

The terminal $t_{1/2}$ of linagliptin was similar in all groups, at 37–49 h.

CD 1790 was only quantifiable for a short time period, and therefore no estimation of terminal $t_{1/2}$ was made for this metabolite. Nonetheless, increases in C_{max} and AUC_{0-72h} for CD 1790 were observed at both linagliptin dose levels. Dose-normalised C_{max} for CD 1790 increased by a factor of 8.2 between linagliptin doses of 1 and 15 mg/kg, while dose-normalised AUC_{0-72h} increased by a factor of approximately 11 between the lower and higher doses.

As with the parent compound, pre-treatment with zosuquidar trihydrochloride resulted in increases in C_{max} and AUC_{0-72h} of CD 1790. The extent of this increase was related to the dose of linagliptin administered, with a much less pronounced effect observed with the higher dose. In contrast, the ratio of C_{max} measurements for linagliptin to CD 1790 were not significantly different between the lower and higher doses of linagliptin, and were not affected by pre-treatment with zosuquidar trihydrochloride.

Within 24 h after i.v. administration of 1 mg/kg [^{14}C]linagliptin, a mean of 28.3% of the total administered dose was excreted in the urine, and 49.0% of the administered dose was excreted in the bile (Table 2). A total of 11.7% of the dose was excreted directly into the gut lumen (2.1% in faeces and 9.6% recovered in the gut contents). Therefore, the total recovery of radioactivity in the excreta, including gut content, was 89.0% of the administered dose. Fig. 2 shows the biliary excretion of [^{14}C]linagliptin, most of which occurred in the first 6–8 h after i.v. bolus administration.

4. Discussion

The findings of these two studies extend previous understanding of the bioavailability and route of elimination of linagliptin.

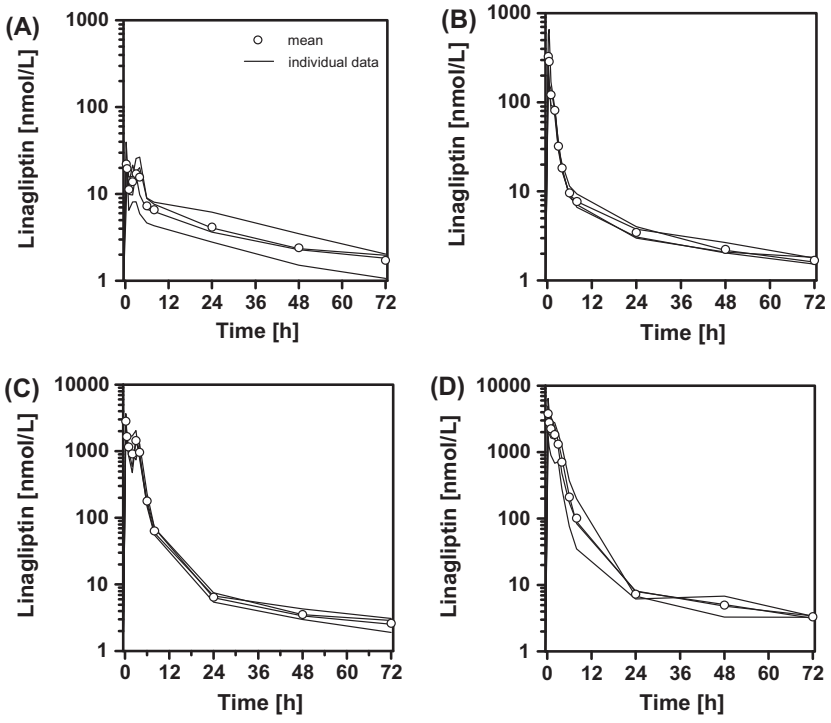

Fig. 1. Individual and mean plasma concentrations of linagliptin in male rats, after single oral administration of a 2.12 μmol/kg (A and B) or 31.8 μmol/kg dose (C and D), without (A and C) or with (B and D) zosuquidar trihydrochloride pre-treatment.

Table 1
Pharmacokinetic parameters for linagliptin and its metabolite, CD 1790.

Parameter	Group 1 2.12 μmol/kg linagliptin	Group 2 2.12 μmol/kg linagliptin + zosuquidar trihydrochloride	Group 3 31.8 μmol/kg linagliptin	Group 4 31.8 μmol/kg linagliptin + zosuquidar trihydrochloride
Linagliptin				
C_{max} (nmol/L) (SD)	25.5 (9.68)	348 (209)	2820 (668)	3810 (2260)
T_{max} (h)	0.75	0.31	0.25	0.25
C_{max}/dose, (nmol/L)/(μmol/kg)	12.0	164	88.7	120
AUC_{0-72h}/dose, (nmol h/L)/(μmol/kg)	147	309	227	309
$AUC_{0-\infty}$/dose, (nmol h/L)/(μmol/kg)	192	364	231	314
Extrapolated $AUC_{72-\infty}$/dose (%)	23.5	15.7	1.8	1.6
$t_{1/2}$ (h)	39.8	48.6	36.7	34.8
CD 1790				
C_{max} (nmol/L) (SD)	0.93 (0.24)	6.87 (2.32)	114 (22.8)	158 (72.2)
T_{max} (h)	0.25	0.44	0.5	1.0
C_{max}/dose, (nmol/L)/(μmol/kg)	0.44	3.24	3.59	4.95
AUC_{0-72h}/dose, (nmol h/L)/(μmol/kg)	1.00	5.66	10.5	18.2
C_{max} ratio linagliptin:CD 1790 (%)	3.5	2.6	4.1	4.5
AUC_{0-72h} ratio linagliptin:CD 1790 (%)	0.6	2.0	4.6	5.8

Table 2
Cumulative excretion of radioactivity after single i.v. bolus administration of [^{14}C]linagliptin to male bile-cannulated rats ($n = 4$).

Sample	Time interval after dosing (h)	Excretion of radioactivity (% of dose)
Urine	0–8	19.9
	0–24	23.2
Faeces	0–24	2.1
Total gut content	0–24	9.6
Bile	0–6	41.3
Total excretion		
Urine (including cage-washings)	0–24	28.3
Faeces and gut content	0–24	11.7
Bile	0–24	49.0
Total recovery	0–24	89.0

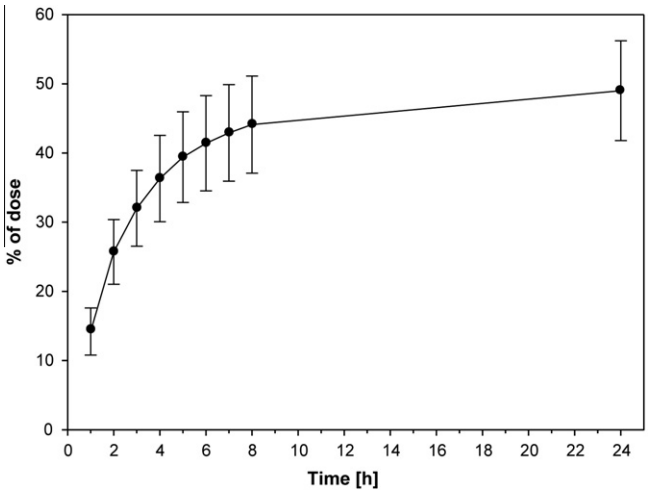

Fig. 2. Cumulative biliary excretion (determined as linagliptin-derived radioactivity) after single i.v. bolus administration of [^{14}C]linagliptin in male rats (mean and SD).

The impact of P-gp-mediated intestinal transport on drug absorption and disposition has frequently been assessed by selective inhibition by zosuquidar trihydrochloride (Starling et al., 1997). For linagliptin, the experiments with zosuquidar trihydrochloride show that inhibition of intestinal P-gp increases the bioavailability of orally administered linagliptin, resulting in a substantial increase in its plasma concentrations. This finding indicates that the oral bioavailability of linagliptin may be limited by P-gp-mediated efflux transport, a mechanism known to have similar effects on several other drugs by actively transporting them into the gut lumen (Stephens et al., 2002).

In the bioavailability study, the increase in C_{max} after P-gp inhibition was dependent on the oral dose of linagliptin, being particularly marked at the lower linagliptin dose (14-fold increase), although the increase in AUC_{0-72h} was only approximately 2-fold at this dose. This finding could be a reflection of the non-linear kinetics and disposition of linagliptin (Fuchs et al., 2009a; Retlich et al., 2009), leading to an over-proportional increase in these parameters after its oral administration.

As linagliptin is known to be a P-gp substrate (Boehringer Ingelheim, Data on File), the observation that the effects of P-gp inhibition by zosuquidar trihydrochloride were more pronounced at the lower linagliptin dose than with the higher dose could be a result of saturation of P-gp at higher linagliptin doses, resulting in smaller increases in the observed C_{max} and AUC_{0-72h} of linagliptin by zosuquidar trihydrochloride pretreatment. As a consequence, the absorption of linagliptin might be enhanced at high doses. This could also partly explain the previously reported non-linear kinetics of linagliptin with an over-proportional increase of the $AUC_{0-\infty}$ after oral dosing of 50–600 mg in humans (Hüttner et al., 2008).

The terminal $t_{1/2}$ of linagliptin observed was similar to that reported previously in rats (36 h) (Deacon and Holst, 2010). The $t_{1/2}$ of linagliptin was found to be similar in all treatment groups, regardless of whether or not animals had been pre-treated with zosuquidar trihydrochloride.

The cytochrome P450 system (CYP3A4) is involved in the formation of CD 1790 in humans (Blech et al., 2010); similarly, it is assumed that the metabolite is generated in rats by a CYP3A. Consistent with previous observations, zosuquidar trihydrochloride appears to selectively inhibit intestinal P-gp in the absence of inhibition of CYP3A at the applied dosing regimen as evidenced by the similar CD 1790 to linagliptin ratios for both C_{max} and AUC_{0-72h}, with or without pre-treatment with zosuquidar trihydrochloride in the bioavailability study. Thus, this study shows that intestinal P-gp-mediated efflux has a role in limiting the absorption of oral linagliptin, and suggests that saturation of P-gp at high doses of linagliptin might partly account for the non-linear oral pharmacokinetics of the drug.

In a previous study of repeated oral dosing of [^{14}C]linagliptin (2 mg/kg) to rats, 89.9% of the administered dose was recovered

in the faeces (Fuchs et al., 2009a), which is consistent with the finding in the present study, where the experiments on intestinal secretion showed that the majority of the administered i.v. dose was recovered in bile, faeces and gut content (60.7%). Furthermore, the observation that 24 h after dosing, biliary excretion of linagliptin had increased to 49.0% (from 41.3% at 6 h), shows that only a further 16% of the total dose of linagliptin was excreted with the bile between 6 and 24 h after i.v. dosing. This suggests, therefore, that following i.v. administration of a single dose, the biliary excretion of linagliptin is largely complete 6 h after dosing. In view of the long terminal $t_{1/2}$ of linagliptin (Hüttner et al., 2008), it is possible that the total biliary excretion of linagliptin, following a single i.v. dose, could be substantially higher than observed in this study. This is because the strong but reversible binding of linagliptin to DPP-4 in the plasma and tissues means that a proportion of the administered dose is not directly available for elimination, leading to a long terminal $t_{1/2}$ and the possibility of delayed biliary excretion of some of the administered linagliptin dose (Fuchs et al., 2009a; Retlich et al., 2009). The binding capacity of DPP-4 is limited and becomes saturated at low doses (above 0.01–0.1 mg/kg in rats), indicating that accumulation of linagliptin is unlikely, despite the persistence of a minor proportion of the dose in the body (Fuchs et al., 2009a). The findings of this study, therefore, indicate that biliary excretion is the major route of elimination of linagliptin, with around half (49%) of the administered dose being recovered in the bile.

Only a small fraction (2%) of the administered linagliptin dose was excreted in the faeces of rats with biliary cannulation within 24 h after administration, with an additional 10% observed in the gut contents, indicating that around 12% of the administered dose was directly secreted into the gut, independently of biliary excretion. As the bioavailability study with and without P-gp inhibition showed, P-gp in the gut limits the oral bioavailability of linagliptin; it is therefore likely that active P-gp-mediated transport is involved in the efflux of linagliptin from the blood into the gut. The biliary excretion and intestinal secretion study showed a direct intestinal excretion of approximately 12% of the administered i.v. dose of linagliptin into the gut, for which P-gp is also likely to be responsible.

The urinary excretion of linagliptin, after bolus injection of 1 mg/kg, was just over 20%, compared with just 0.96% urinary excretion after oral administration of 2 mg/kg, as has been previously observed in rats (Fuchs et al., 2009a). This difference can be explained by the concentration-dependent binding of linagliptin to its DPP-4 target (Retlich et al., 2009), and the observation that the urinary excretion of linagliptin is dependent on the plasma concentration, as a result of this saturable binding in plasma (Fuchs et al., 2009b). With increasing doses of linagliptin, the binding of the drug to DPP-4 in the plasma and tissues becomes saturated, leading to dose-dependent renal excretion at linagliptin levels above those needed to saturate DPP-4 binding. Therefore, the relatively high proportion of the administered dose that was excreted in the urine, in the present study, is likely to result from the high initial plasma concentrations of linagliptin following i.v. bolus administration. Based on previous experiments in rats, the percentage of an orally administered dose of linagliptin eliminated by urinary excretion is expected to be negligible (Fuchs et al., 2009a). As inhibition of DPP-4 can be achieved at low doses in humans (5 mg, once daily), urinary excretion of linagliptin would also be expected to be minimal, and this has been confirmed in healthy subjects at low doses of 2.5 and 5 mg per subject (Hüttner et al., 2008) and in patients with type 2 diabetes at 5 mg per subject (Heise et al., 2009).

The findings of these two studies show that the bioavailability of orally administered linagliptin is enhanced by inhibition of intestinal P-gp, indicating that this transport system plays a role in limiting the uptake of linagliptin from the intestine. Systemically available linagliptin is mainly excreted with the bile in rats, whilst some (~12% of an i.v. dose) is secreted directly into the gut, independent of biliary excretion, and it is likely that P-gp-mediated efflux is involved in this latter excretory pathway. The findings of these studies, combined with others, show that the largely non-renal excretion route of linagliptin does not involve major metabolism in the liver. This primarily non-renal excretion of linagliptin is likely to be an important benefit to patients with type 2 diabetes, a population that has a high risk and prevalence of renal insufficiency.

Authorship contributions

- Participated in research design: H. Fuchs, H.-D. Held
- Conducted experiments: lab co-workers of H. Fuchs, H.-D. Held, F. Runge: Isabelle Glockmann, Cornelia Ackermann, and Thomas Sauter (no co-authorship)
- Contributed new reagents or analytic tools: F. Runge
- Performed data analysis: H. Fuchs, H.-D. Held
- Wrote or contributed to the writing of the manuscript: H. Fuchs, H.-D. Held, F. Runge
- Other: (e.g. acquired funding for the research): none

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