Absorption, metabolism and excretion of [^{14}C]-gemigliptin, a novel dipeptidyl peptidase 4 inhibitor, in humans

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INTRODUCTION

Dipeptidyl peptidase 4 (DPP-4) inhibitors are increasingly used for the treatment of type 2 diabetes. DPP-4 inhibitors act by blocking degradation of active glucagon-like peptide 1, which is an incretin hormone stimulating insulin secretion and inhibiting glucagon secretion (Drucker & Nauck, 2006). Gemigliptin (Zemiglo, also known as LC15-0444) is a newly developed, oral, highly selective and potent DPP-4 inhibitor. Gemigliptin was first approved in Republic of Korea (2012).

METHODS

The study was conducted in six healthy male Caucasian subjects (36-54 years old, 73.4-113.8 kg body weight) at Quotient Clinical (Nottingham, UK). Written informed consent was obtained from all subjects, and the protocol and associated documents were approved by Welwyn Clinical Pharmacology Ethics Committee (Hatfield, UK). In addition, the study was performed according to the ethical principles outlined in Declaration of Helsinki and its amendments.

Subjects were admitted to the clinical unit in the day before dosing (Day 1) and were resident in the clinic for eight days after dosing. After an overnight fast, all six subjects received a single oral capsule containing 50 mg [^{14}C]gemigliptin and 5.4MBq [^{14}C] with 240mL water.

Samples for the analysis of gemigliptin in plasma, total radioactivity in whole blood and plasma, metabolite profiling and identification in plasma, and for haematology and clinical chemistry safety assessments, were taken at specified time points. Urine and faecal samples for analysis of total radioactivity were also taken at specified time points.

OBJECTIVES

The primary objectives of the study were:

- To determine the mass balance after a single oral dose of [^{14}C]gemigliptin
- To determine the routes of [^{14}C]gemigliptin metabolism and excretion
- To provide plasma, urine and faeces samples for metabolite profiling
- To assess the pharmacokinetics (PK) of [^{14}C]gemigliptin in plasma, following a single oral dose

The secondary objectives of the study were:

- To identify the structure of any significant metabolites
- To provide additional safety and tolerability information for gemigliptin

RESULTS AND DISCUSSION

Mass balance

Following oral administration of 50 mg [^{14}C]gemigliptin (5.4 MBq) to healthy male subjects, total 90.5 % of administered dose was recovered in the urine and feces over the study period. Mean cumulative recovery of radioactivity was 63.4 % from the urine and 27.1 % from the feces until 192 hr post dose. Approximately half of the dose was recovered within 48-hr post dose.

Pharmacokinetics of gemigliptin and total radioactivity

Concentration-time profiles of plasma gemigliptin and plasma/blood total radioactivity are presented in Figure 1. Maximum plasma concentration (Cmax) was 43.5 ng/mL for gemigliptin at 4.5 hr post dose and 84.5 ng-eq/mL for total radioactivity at 5 hr post dose. Comparison of area under the time-concentration curve from time zero to 24 hr post dose (AUC0–24 h) for individual subjects showed that gemigliptin accounted for 28% to 48% of total radioactivity in plasma, suggesting extensive formation of radiolabelled metabolites or breakdown products. The half-life (t1/2) of gemigliptin was 30.8 hr, while terminal slope of total radioactivity was not reliably estimated. Plasma concentration-time profiles suggested relatively slow decline of total radioactivity compared to gemigliptin. At all time points, total radioactivity concentrations in plasma and whole blood were comparable. Mean Cmax and AUC0–24hr for blood total radioactivity were 97 % and 92 % of those for plasma total radioactivity, indicating equal distribution between plasma and cellular components of whole blood.

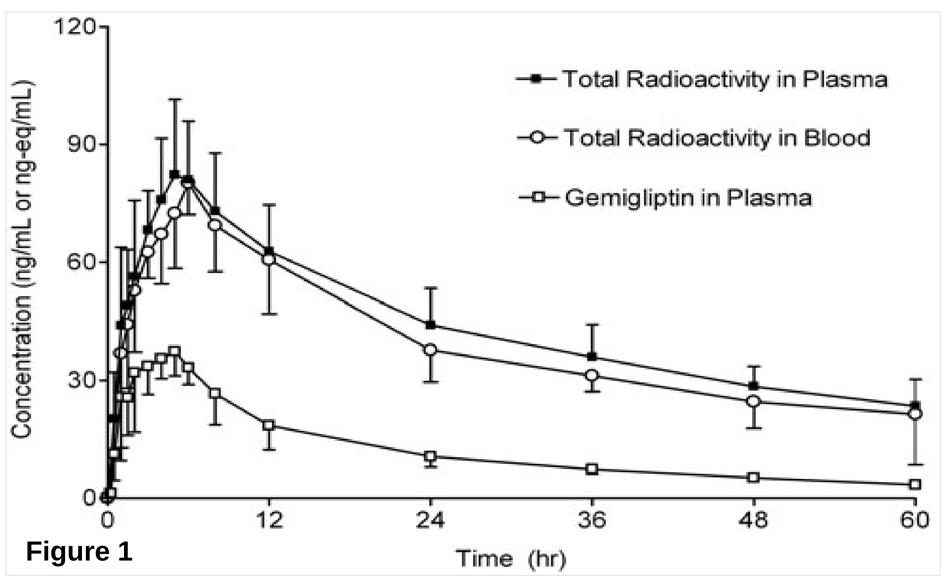


Figure 1

Metabolite profiling

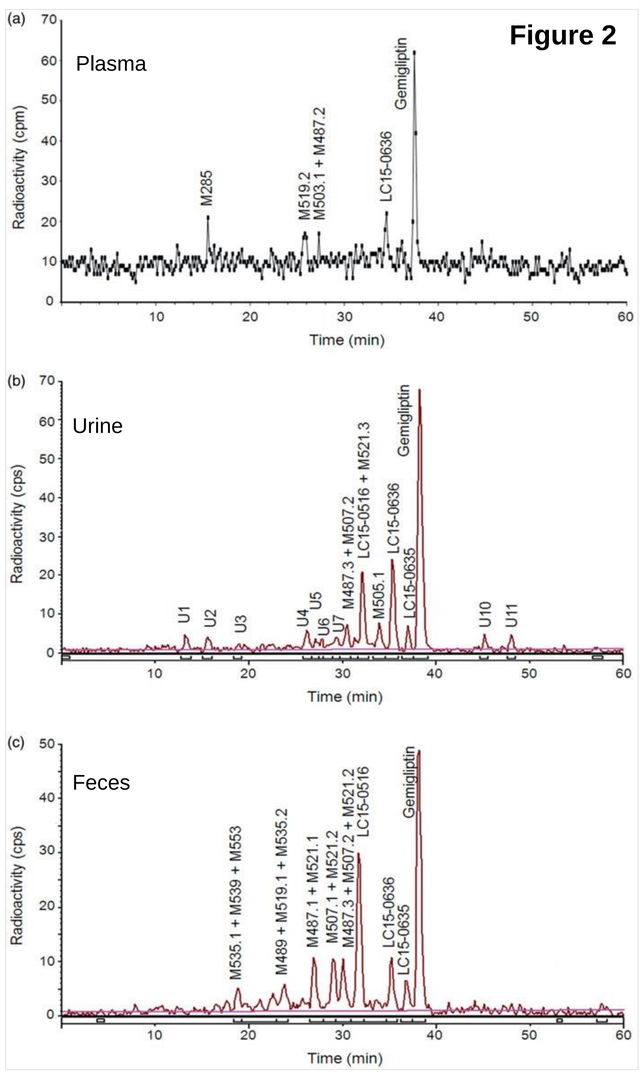
Representative radiochromatograms of pooled plasma (2hr), urine (48 – 72 hr) and feces (72 - 96 hr) samples are shown in Figure 2.

The major component in the systemic circulation was parent drug, accounting for 67.2 % - 100 % of plasma. radioactivity. Six metabolites were detected in at least one plasma sample. LC15-0636 was the most abundant metabolite in plasma, accounting for 9.1 % - 17.5 % of plasma radioactivity.

Parent drug was the most abundant component in urine collected 0-72 hr post dose, accounting for 44.8 % - 67.2 % of urinary radioactivity (32.6% of administered dose). LC15-0636, LC15-0516 and LC15-0635 accounted for 12.3 % - 14.3 %, 4.0 % - 11.9 % and 2.1 % - 2.9 % of urinary radioactivity respectively.

In feces collected 24 - 144 hr post dose, parent drug accounted for 27.7 % - 51.8 % of fecal radioactivity (16.5% of administered dose). LC15-0516, LC15-0636 and LC15-0635 accounted for 12.9 % - 21.7 %, 3.4 % - 7.1 % and 3.2 % - 4.3 % of fecal radioactivity respectively.

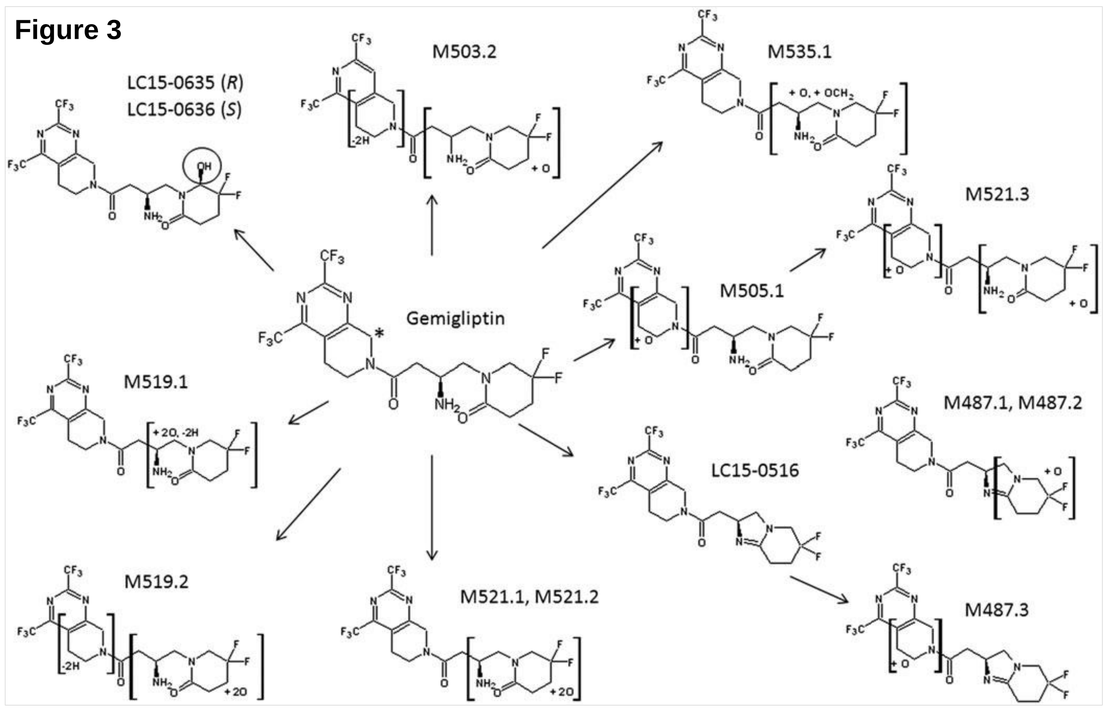
Figure 2



Identification of metabolite chemical structure

Putative and identified metabolites of [^{14}C]gemigliptin in human plasma, urine and feces are summarized in Table 4. A metabolic pathway of [^{14}C]gemigliptin in human is proposed in Figure 3.

Figure 3



CONCLUSIONS

[^{14}C]gemigliptin was well absorbed following oral administration and subsequently eliminated through balanced pathways of metabolism and urinary/fecal excretion. Mean cumulative recovery of radioactivity was 63.4 % from the urine and 27.1 % from the feces, over the duration of the study. In plasma, gemigliptin was the major circulating component with only 1 metabolite that accounted for more than 10 % drug related material. This metabolite was LC15-0636, which is formed by CYP3A4, and is an active metabolite with a potency 2 times that of gemigliptin (Noh et al, 2009).

REFERENCES

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