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Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment

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Abstract Objective: The primary objective of this single-centre, open-label, parallel-group study was to evaluate the pharmacokinetics and safety profile of the prandial glucose regulator repaglinide, following single and multiple dosing, in patients with type 2 diabetes with and without varying degrees of renal impairment. Methods: The study comprised three screening visits, followed by a 7-day inpatient period. Thirty-four patients, with normal renal function (n = 12), mild-to-moderate renal dysfunction (n = 12) or severe renal dysfunction (n = 10), received a single 2-mg dose of repaglinide on day 1, followed by preprandial 2-mg doses with main meals (breakfast, lunch and dinner) on each of days 2-4. A final 2-mg dose of repaglinide was administered on day 5. Results: Patients with mild-to-moderate renal impairment showed no significant differences in the pharmacokinetics of repaglinide, compared with patients with normal renal function. In the group of patients with severe renal dysfunction, the main pharmacokinetic finding was a longer half-life after multiple dosing. Rates of minor hypoglycaemia were similar in patients with severe, mild-to-moderate and no renal dysfunction. No major hypoglycaemic episodes occurred. Conclusion: Patients with type 2 diabetes and mild or moderate impairment of renal function may be treated with repaglinide without special precautions. If repaglinide is used in patients with severely impaired renal function, dose adjustment may be necessary if indicated by blood glucose measurements.

Keywords Type 2 diabetes · Repaglinide · Renal function

Introduction

Type 2 diabetes is a serious, progressive metabolic disease, which when poorly controlled is characterised by acute and chronic hyperglycaemia. This hyperglycaemia is the central factor in a constellation of complications that include cardiovascular disease, retinopathy, nephropathy and neuropathy [1]. It is established that good control of type 2 diabetes can significantly reduce the risk of development or progression of many of these complications [2, 3, 4]. However, the presence of some complications itself hinders our ability to control the disease. In particular, renal dysfunction, whether resulting from diabetic nephropathy or other causes, may reduce the utility of antidiabetic drugs that are metabolised and eliminated via the kidneys, thereby hindering their ability to control diabetes.

Repaglinide, a carboxamidomethyl benzoic acid derivative, is a new antidiabetic agent which stimulates insulin secretion from the pancreatic beta-cells [5]. Like the sulphonylureas, repaglinide acts by depolarising the pancreatic beta-cell membrane by blocking ATP-gated potassium channels. However, in contrast to the sulphonylureas, repaglinide does not stimulate insulin release independently of its effects on beta-cell potassium channels, and does not inhibit insulin biosynthesis [6, 7, 8, 9]. Furthermore, repaglinide augments insulin release from pancreatic islets in vitro only in the presence of glucose [6, 10].

In addition to its mechanistic differences, repaglinide is differentiated from other hypoglycaemic agents such as sulphonylureas by its rapid and short duration of action and by its mechanism of elimination [5]. Repaglinide was developed for use as a prandial glucose regulator in a flexible mealtime dosing schedule (‘one meal, one dose; no meal, no dose’). [6, 11]. Following oral administration of repaglinide at clinically relevant doses, peak serum levels are reached within 30–60 min [5, 12, 13]. Repaglinide is almost completely (98%) bound to plasma proteins, has a low tissue distribution
and undergoes a very rapid elimination from the body, with a plasma half-life (t_{1/2}) of less than 1 h [13]. Following its breakdown in the liver, by oxidative biotransformation via the cytochrome P450 isoform CYP3A4 or by direct conjugation with glucuronic acid, the metabolites of repaglinide are excreted via the bile: only 8% of a given dose of repaglinide is excreted via the urine [5]. The elimination profile of repaglinide suggests that it may be well suited for use in patients with type 2 diabetes and renal impairment. This study was designed to evaluate the pharmacokinetics of repaglinide in patients with type 2 diabetes, with and without varying degrees of renal impairment.

**Materials, methods and subjects studied**

The study was a single-centre, open-label, parallel-group pharmacokinetic trial, approved by the Ethics Committee of the Medical Faculty of the Ruprecht-Karls-University, Heidelberg, and performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Patients who took part in the study gave their written informed consent before participating in any study-related activities. All patients had had type 2 diabetes for at least 1 year and were aged 45–75 years. Exclusion criteria included the presence of type 1 or any secondary diabetes, severely unstable type 2 diabetes, glycated haemoglobin (HbA_{1c}) >12%, creatinine clearance (Cl_{CR}) judged to be clustered within parts of the Cl_{CR} ranges, rapidly changing renal function or previous kidney transplantation, hepatic disease, unstable proliferative retinopathy, cardiac problems, severe uncontrolled hypertension, pregnancy and ongoing corticosteroid therapy. Patients with type 2 diabetes who were being treated with diet, insulin or oral hypoglycaemic agents were all eligible for entry.

The study comprised three screening visits and the last two were performed 2–26 days before day 1 of the inpatient period and were used to measure Cl_{CR} over two 24-h urine sampling periods by the Jaffe method. Screening was followed by a 7-day inpatient and follow-up period. Patients were stratified into three groups based on degree of renal dysfunction: normal renal function (Cl_{CR} > 90 ml/min), mild-to-moderate impairment (80 ≥ Cl_{CR} ≥ 40 ml/min) or severe impairment (40 > Cl_{CR} ≥ 20 ml/min). Efforts were made to achieve an equal distribution of age and sex within the groups. Patients taking insulin reduced their doses during the inpatient period and those receiving oral antidiabetic agents stopped their treatment 7 days prior to the inpatient period.

**Dose regimen**

Patients received a single 2 mg repaglinide tablet on the morning of day 1 of their inpatient period, while fasting from the previous evening until 4 h post-dosing. On days 2–4, patients received three 2-mg doses taken before main meals. On day 5, a final 2-mg dose of repaglinide was administered, in the fasting state as on day 1. On each of days 1 and 5, patients voided their bladders immediately before administration of repaglinide, and maintained a water intake of 120 ml/h until noon.

**Pharmacokinetic evaluation**

Pharmacokinetic parameters for repaglinide, area under the curve (AUC_{0–∞}), terminal half-life (t_{1/2}) or, equivalently, terminal elimination rate constant (t_{2}) maximum concentration (C_{max}) and time to maximum concentration (t_{max}), were calculated from serum repaglinide profiles obtained on day 1 and day 5. On each day, samples for repaglinide and glucose were taken at 15-min intervals for the first 90 min after dosing, at 30-min intervals for a further 90 min and at 240 min post-dose. Repaglinide samples were continued hourly until 6 h, two-hourly until 12 h, and thereafter at 16, 24, 36 and 48 h post-dose. AUC was calculated using the trapezoidal rule, where values below LoQ were set to 1/2*LoQ.

Samples were analysed for repaglinide using a validated liquid chromatography mass spectrometry assay (MRM mode, m/z 453.1→320.1 following solid-phase extraction; limit of quantification 0.200 ng/ml). C_{max} and t_{max} were recorded directly from the concentration–time profiles, while t_{2} was determined from the terminal part of the concentration profiles using in each case the five time points immediately preceding the last decreasing concentration occurring between t_{max} and 2 h. Terminal half-life was calculated from the measured value of t_{2}.

**Safety evaluation**

Adverse events, including hypoglycaemic episodes, were recorded. Hypoglycaemic episodes were classified as minor (no third-party assistance required), major A (third-party help necessary) or major B (requiring intravenous glucose or glucagon). General physical examinations, including assessment of vital signs, were undertaken during screening, inpatient period and follow-up reviews. Other assessments included haematological and biochemical laboratory tests and electrocardiograms (ECGs). Blood glucose measurements were made from blood samples taken during the first 4 h after dosing on days 1 and 5, and as eight-point profiles using a standard (One Touch Basic; LifeScan) glucose meter on days 2–4. Serum repaglinide samples were analysed by a validated liquid chromatography mass spectrometry assay (MRM mode, m/z 453.1→320.1) following solid phase extraction [13]. The limit of quantification of the assay was 0.200 ng/ml.

The safety screening tests of haematology and biochemistry were done at the first screening visit and repeated on the day after treatment period (day 7) as part of the follow-up examinations. They comprised RBC, WBC (including leukocytes, lymphocytes, neutrophils, basophils, eosinophils and monocytes) platelets, sodium, chloride, potassium, calcium, blood glucose, inorganic phosphate, alkaline phosphatase, gamma-GT, aspartate aminotransferase, alanine aminotransferase, total bilirubin, activated creatine kinase, LDH, creatinine, urea, uric acid, total cholesterol, triglycerides, albumin and total protein.

**Statistical analysis**

Non-parametric monotone regression analysis was used to test for a correlation between Cl_{CR} and either AUC or t_{1/2}. Population means of log(AUC) and t_{2} were estimated for each combination of renal function and day of study, using an ANOVA including overall mean, fixed renal function, fixed day, fixed interaction between renal function and day, random patient and random error.

**Results**

A total of 34 patients entered and completed the study, of whom 12 had no renal dysfunction, 12 had mild or moderate renal dysfunction and 10 had severe renal dysfunction as defined by measurement of Cl_{CR}. Patients in the three renal function groups were similar in terms of weight, height, body mass index and HbA_{1c}, and there was a fairly even sex distribution between the groups (Table 1). The patients with severely impaired renal function were slightly older with a longer history of diabetes, compared with the other two groups. Hepatic function was identical between groups both at entry and on completion of the study, with no differences between