Effect of Renal Insufficiency on the Pharmacokinetics of Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor

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Sitagliptin is an oral, once-daily, potent, and highly selective dipeptidyl peptidase–4 inhibitor for the treatment of type 2 diabetes (1). In subjects with normal renal function (creatinine clearance >80 ml/min), 75–80% of an oral dose was excreted unchanged in urine. Renal clearance was ~350 ml/min, indicating that active secretion of sitagliptin rather than only filtration is involved in renal excretion. Thus, renal excretion is the primary mechanism of elimination for sitagliptin (2). The purpose of this study was to evaluate the pharmacokinetics of single doses of sitagliptin in patients with various degrees of renal insufficiency (RI).

RESEARCH DESIGN AND METHODS

— This was an open-label, two-part study in 30 otherwise healthy male and female subjects (18–75 years of age) with BMI ≤40 kg/m^2. Subjects were assigned to one of five groups (n = 6/group), based on the following criterion for degree of RI: mild (creatinine clearance 50–80 ml/min), moderate (30–50 ml/min), severe (<30 ml/min), end-stage renal disease (ESRD) on hemodialysis, and normal (>80 ml/min). Healthy subjects (n = 145) from 11 other studies were included in a historical control group to supplement those studied here. Creatinine clearance values were based on measured 24-h urinary creatinine excretion (this study) or calculated using the Cockroft-Gault formula (historical controls). Because sitagliptin plasma concentrations were expected to increase with RI, a 50-mg dose was expected to be well tolerated in the event of substantial increases in drug concentrations. All subjects provided written informed consent. The protocol was approved by investigational review boards and carried out in accordance with the principles of the Declaration of Helsinki.

In Part I, 18 patients with mild to severe RI and 6 healthy concurrent control subjects received a single 50-mg dose of sitagliptin followed by 96 h of plasma sampling and 48 h for urine collection for sitagliptin concentrations. During period 1 of Part II, patients with ESRD requiring hemodialysis received a single 50-mg dose of sitagliptin 48 h before their normally scheduled hemodialysis session. Following period 1 and at least a 1-week wash off, the same ESRD patients received a single 50-mg sitagliptin dose 4 h before their hemodialysis session to quantify the amount of sitagliptin removed by dialysis. Plasma and dialysate samples were collected at prespecified times up to 96 h following dosing.

Pharmacokinetic analysis

Sitagliptin was measured in plasma, urine, and dialysate samples by mass spectrometry detection following specialized high-performance liquid chromatography with an internal standard (3). Calculations for pharmacokinetic parameters were completed, according to established methods (4,5). The area under the sitagliptin plasma concentration curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) was considered the most relevant pharmacokinetic parameter because it provides an estimate of the plasma drug exposure at steady state.

Safety

Safety and tolerability were assessed from adverse experiences and measurements of vital signs, 12-lead electrocardiograms, and laboratory safety parameters. Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug.

Statistical analyses

Since sitagliptin $AUC_{0-\infty}$ had been shown to be dose proportional following single oral doses from 25 to 800 mg (2,5), $AUC_{0-\infty}$ values for healthy subjects from clinical studies were adjusted based on a 50-mg dose. Additionally, because these results were similar to the six concurrent controls, these data were pooled for the analysis. Historical data for other pharmacokinetic parameters were limited to those from a 50-mg dose group (Table 1). ANCOVA models containing creatinine clearance as a continuous or categorical variable and covariates of age, sex, and weight were both used for analysis of pharmacokinetic parameter data. Based on the apparent wide therapeutic index of sitagliptin (2,5,6), an increase in plasma sitagliptin exposure (i.e., $AUC_{0-\infty}$) of less than twofold was not considered clinically meaningful.

RESULTS

— All patients completed the study. Using the continuous model,

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Abbreviations: $AUC_{0-\infty}$, area under the sitagliptin plasma concentration curve from time zero to infinity; ESRD, end-stage renal disease; RI, renal insufficiency.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Summary statistics of sitagliptin pharmacokinetic parameters following administration of single oral doses of 50 mg sitagliptin in patients with varying degrees of renal function and healthy subjects with normal renal function*

	Pooled normal (>80 ml/min)		Mild (50–80 ml/min)		Moderate (30–50 ml/min)		Severe (<30 ml/min)		ESRD (requiring hemodialysis)*	
n	58–151†		6		6		6		6	
	Mean‡	Mean‡	GMR (90% CI)§	Mean‡	GMR (90% CI)§	Mean‡	GMR (90% CI)§	Mean‡	GMR (90% CI)§
$AUC_{0-\infty}$ (μM·hr)‖	4.40	7.09	1.61 (1.43–1.81)	9.96	2.26 (2.02–2.53)	16.6	3.77 (3.37–4.22)	19.8	4.50 (4.03–5.03)
C_{max} (nM)	391	527	1.35 (1.15–1.58)	560	1.43 (1.23–1.67)	684	1.75 (1.51–2.03)	556	1.42 (1.22–1.65)
$C_{24\ h}$ (nM)	43.7	83.3	1.91 (1.60–2.28)	129	2.96 (2.50–3.50)	228	5.22 (4.42–6.16)	260	5.95 (5.04–7.02)
T_{max} (h)	3.0	3.0	*P* = 0.303	3.0	*P* = 0.771	3.5	*P* = 0.696	5.0	*P* = 0.027
Terminal $t_{1/2}$ (h)	13.1	16.1	*P* = 0.011	19.1	*P* < 0.001	22.5	*P* < 0.001	28.4	*P* < 0.001
$f_{e\,0-\infty}$ ¶	0.76	0.84	0.09 (0.01–0.16)	0.64	−0.12 (−0.18 to −0.05)	0.52	−0.24 (−0.30 to −0.17)	NA	NA#
Cl_R (mL/min)	339	242	0.71 (0.63–0.81)	126	0.37 (0.33–0.42)	60.2	0.18 (0.16–0.20)	NA	NA#

*Hemodialysis at 48 h postdose in subjects with ESRD. †Sample size was 151 for $AUC_{0-\infty}$ and 58 for $f_{e\,0-\infty}$, and Cl_R and 82 for the rest. Healthy control data included data from various Phase I safety/pharmacokinetic/pharmacodynamic protocols; Mean values for normal subjects from protocol 008 included in pooled sample of normal subjects: $AUC_{0-\infty}$, 4.59; C_{max}, 347; $C_{24\ h}$, 49.5; T_{max}, 4.5; $t_{1/2}$, 15.1; $f_{e\,0-\infty}$, 0.76; and Cl_R, 341. ‡Geometric least-squares mean for $AUC_{0-\infty}$, C_{max}, $C_{24\ h}$, and Cl_R; median for T_{max}; harmonic mean for terminal $t_{1/2}$; arithmetic mean for $f_{e\,0-\infty}$. §GMR, geometric mean ratio; *P* values reported for T_{max} and $t_{1/2}$; Arithmetic mean difference and 90% CIs reported for $f_{e\,0-\infty}$. ‖Area under the plasma level vs. time curve from time zero extrapolated to infinity from the last measured time point and dose-adjusted to 50 mg (single oral doses of 25, 50, 100, 200, 400, 600, and 800 mg). ¶Fraction of dose excreted unchanged in urine extrapolated to infinity. #Urine was not collected from subjects with ESRD. $C_{24\ h}$, concentration at 24 h; C_{max}, highest concentration observered; Cl_R, renal clearance.

increases in sitagliptin $AUC_{0-\infty}$ were less than twofold for mild RI patients relative to the normal renal function controls (Table 1). From the categorical analysis, increases in sitagliptin $AUC_{0-\infty}$ were ~2.3-fold higher for moderate RI patients. Increases in sitagliptin $AUC_{0-\infty}$ were ~3.8-fold higher for severe RI. Increases in sitagliptin $AUC_{0-\infty}$ were ~4.5-fold higher for patients with ESRD. C_{max} was moderately increased, and C_{24} increased as renal function decreased. T_{max} was significantly increased in patients with ESRD, and the terminal $t_{1/2}$ increased with decreasing renal function. Renal clearance of sitagliptin was approximately proportional to creatinine clearance.

The fraction of dose removed by dialysis was small with 13.5 and 3.5% for hemodialysis initiated at 4 and 48 h postdose, respectively. Plasma protein binding was not altered in uremic plasma from the RI patients (median 36%, range 33–40%) as compared with that from concurrent control subjects (median 37%, range 34–43%). Single doses of sitagliptin were well tolerated in this study.

CONCLUSIONS — Based on the present findings, sitagliptin dose adjustments are recommended for patients with moderate or severe RI or ESRD to provide plasma sitagliptin exposure comparable to patients with normal renal function. The recommended sitagliptin dosage adjustments are as follows: no adjustment for patients with mild RI (creatinine clearance 50–80 ml/min), a twofold decrease in the clinical dose of 100 mg q.d. (i.e., 50 mg q.d.) for patients with moderate RI (creatinine clearance 30–50 ml/min) (approximate serum creatinine levels >1.7 and ≤3.0 mg/dl for men and >1.5 and ≤2.5 mg/dl for women), and a fourfold decrease in the clinical dose (25 mg q.d.) for patients with severe RI (creatinine clearance <30 ml/min) or ESRD (approximate serum creatinine levels >3.0 mg/dl for men, >2.5 mg/dl for women, or on dialysis). Moreover, since hemodialysis removed sitagliptin to a modest extent, sitagliptin can be administered without respect to the timing of hemodialysis in patients with ESRD.

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