Effects of Vildagliptin and Metformin on Blood Pressure and Heart Rate Responses to Small Intestinal Glucose in Type 2 Diabetes

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OBJECTIVE

To evaluate effects of vildagliptin and metformin on blood pressure (BP) and heart rate (HR) responses to intraduodenal (ID) glucose in diet-controlled type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study A compared vildagliptin (50 mg) and placebo, given 60 min before a 120-min ID glucose infusion at 2 or 4 kcal/min (ID2 or ID4) in 16 patients. Study B compared metformin (850 mg) and placebo, given 30 min before ID2 over 120 min in 9 patients.

RESULTS

Systolic (P = 0.002) and diastolic (P < 0.001) BP were lower and HR greater (P = 0.005) after vildagliptin compared with placebo, without interaction between vildagliptin and the glucose infusion rate. In contrast, HR was greater after metformin than placebo (P < 0.001), without any difference in systolic or diastolic BP.

CONCLUSIONS

Vildagliptin reduces BP and increases HR, whereas metformin increases HR without affecting BP during ID glucose infusion in type 2 diabetes. These distinct cardiovascular profiles during enteral nutrient exposure may have implications for postprandial hypotension.

Reports of the blood pressure (BP) effects of hypoglycemic agents in clinical studies have typically not discriminated between fasting and postprandial conditions. Exposure of the small intestine to nutrients increases splanchnic blood flow and may reduce BP (1). Postprandial hypotension (a fall in systolic BP [SBP] of ≥20 mmHg within 2 h of a meal) occurs frequently in type 2 diabetes and is associated with syncope, falls, and increased mortality (1). We evaluated effects of the dipeptidyl peptidase 4 inhibitor vildagliptin and metformin on SBP, diastolic BP (DBP), and heart rate (HR) during intraduodenal (ID) glucose infusion in patients with diet-controlled type 2 diabetes, using data collected in two published studies (2,3).

RESEARCH DESIGN AND METHODS

Study A: Vildagliptin

Sixteen subjects (11 male; 65.5 ± 2.4 years; BMI 30.4 ± 1.5 kg/m^2; HbA_{1c} 6.3 ± 0.1% [45.6 ± 1.6 mmol/mol]; diabetes duration 5.1 ± 1.4 years, without evidence of

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autonomic dysfunction) completed the study. Nine subjects were receiving antihypertensive medications, which were withheld for 24 h before each study day. Subjects were studied on four occasions (≥7 days apart) after an overnight fast in randomized, double-blind fashion. On each day, they ingested 50 mg vildagliptin or placebo (t = −60 min), followed by an ID glucose infusion at either 2 or 4 kcal/min (ID2 or ID4; osmolality matched at ~1,390 mOsmol/L using sodium chloride) during t = 0–120 min while lying supine.

Study B: Metformin

Nine males (63.8 ± 2.6 years; BMI 30.4 ± 1.4 kg/m^2; HbA_{1c} 6.6 ± 0.2% [48.9 ± 1.7 mmol/mol]; diabetes duration 3.6 ± 1.3 years; without evidence of autonomic dysfunction) received metformin 850 mg or placebo for 7 days in a double-blind, randomized, crossover design (with a 14-day washout). Three subjects were receiving antihypertensive medications, which were withheld for 24 h before each study day. On day 5 or 8, after an overnight fast, subjects ingested 850 mg metformin or placebo (t = −30 min), followed by an ID glucose infusion at 2 kcal/min (t = 0–120 min).

Informed consent and ethics approval were obtained for both studies. SBP, DBP, and HR were measured every 5 min (DINAMAP ProCare 100 automatic sphygmomanometer; GE Healthcare, Milwaukee, WI). In study A, superior mesenteric artery (SMA) blood flow was also measured by Doppler ultrasound at regular intervals (4).

In study A, areas under the curve for SBP, DBP, HR, and SMA blood flow before and during ID glucose infusion were expressed as mean values over each period. Baseline mean values were analyzed using one-factor repeated-measures ANOVA (SPSS 24; IBM, New York, NY). Mean values during ID infusions were analyzed using two-factor repeated-measures ANOVA, with the glucose infusion rate and treatment (vildagliptin/placebo) as factors. These measures were also analyzed using two-factor repeated-measures ANOVA, with treatment and time as factors. Numbers of subjects in whom SBP fell ≥20 mmHg were compared using McNemar test. In study B, all measures were compared using two-factor repeated-measures ANOVA, with treatment and time as factors. Data are presented as mean values ± SEM. The P values <0.05 were considered significant.

RESULTS

Study A

Prior to ID glucose infusion, SBP, DBP, HR, and SMA blood flow did not differ between study days. During ID glucose infusion, SBP and DBP decreased promptly and recovered slowly thereafter, whereas HR and SMA blood flow increased to a plateau (time effect: $P <$ 0.001) (Fig. 1*A–C*). Mean SBP (P = 0.002) and DBP ($P <$ 0.001) were lower with vildagliptin than placebo, without any difference between ID2 and ID4. HR was higher during ID4 than ID2 (P = 0.003) and further increased with vildagliptin versus placebo (P = 0.005) (Supplementary Fig. 1). SMA blood flow was greater during ID4 versus ID2 (P = 0.018), without any difference between vildagliptin and placebo (Supplementary Fig. 2). Only one subject experienced a fall in SBP ≥20 mmHg on placebo, compared with seven after vildagliptin during ID2 (P = 0.031) and five during ID4 (P = 0.125).

Study B

Basal measures did not differ between the two days. During ID glucose infusion, SBP and DBP decreased and HR increased on both days (time effect: $P <$ 0.001). Neither SBP nor DBP differed between treatments; however, HR was greater with metformin than placebo (treatment effect: $P <$ 0.001) (Fig. 1*D–F*).

CONCLUSIONS

In patients with well-controlled type 2 diabetes without evidence of autonomic dysfunction, acute dosing with vildagliptin lowered SBP and DBP and increased HR, without affecting SMA blood flow, during ID glucose infusion at two rates within the physiological range of gastric emptying (5), whereas metformin

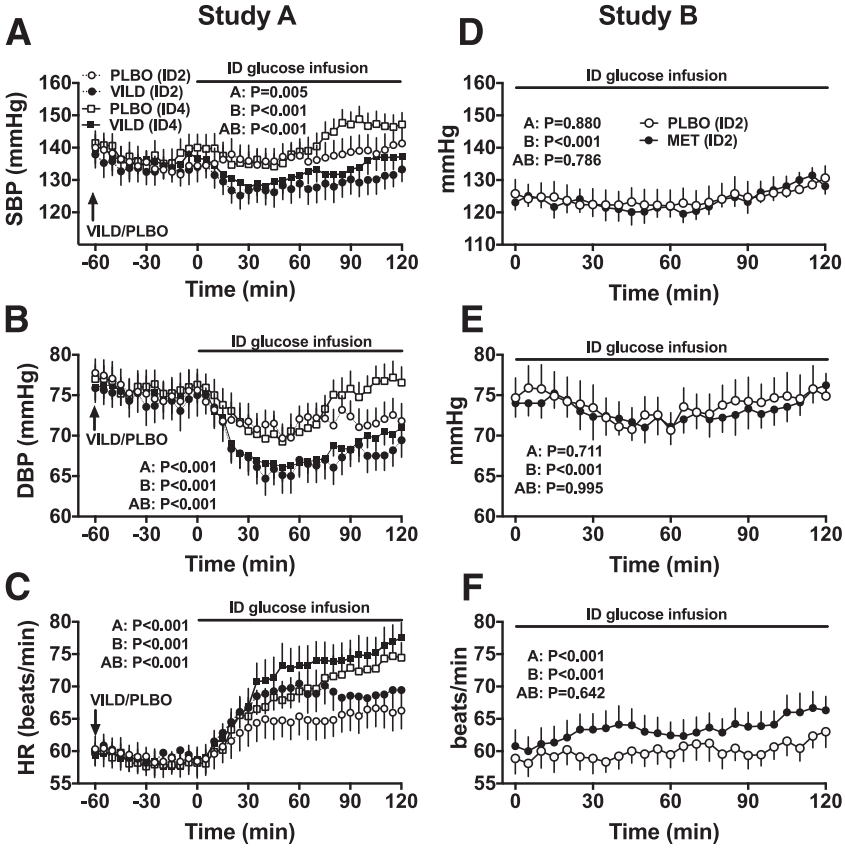

Figure 1—Study A: effects of vildagliptin (VILD) or placebo (PLBO) on SBP (*A*), DBP (*B*), and HR (*C*) before (t = −60 to 0 min) and during (t = 0–120 min) ID glucose infusion at the rate of 2 or 4 kcal/min (ID2 or ID4) in patients with type 2 diabetes (n = 16). Study B: effects of metformin (MET) or PLBO on SBP (*D*), DBP (*E*), and HR (*F*) during an ID glucose infusion at the rate of 2 kcal/min in patients with type 2 diabetes (n = 9). Two-factor repeated-measures ANOVA, with treatment and time as factors, was used to determine statistical significance. Results of ANOVA are reported as P values for differences by treatment (A), differences over time (B), and differences because of interaction between the two factors (AB). Data are mean values ± SEM.

increased HR during ID glucose infusion without affecting BP.

The magnitude of reduction in SBP with vildagliptin during ID glucose infusion was substantial, particularly in terms of the number of subjects experiencing a marked fall in SBP compared with placebo, yet vildagliptin had no effect on cardiovascular measures during fasting. This suggests that the cardiovascular effects of vildagliptin are likely to be mediated by nutrient-induced, cardiovasoactive factors, potentially including glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, peptide YY, stromal cell–derived factor 1α, and brain natriuretic peptide (6). SMA blood flow was not affected by vildagliptin, suggesting that the fall in BP did not reflect a further increase in splanchnic blood pooling.

The clinical implications of the reduction in BP and increase in HR during ID glucose by vildagliptin are uncertain. In general, lowering of BP may be advantageous in patients with type 2 diabetes, but postprandial hypotension is now recognized as an important clinical issue that predisposes to falls, syncope, coronary events, stroke, and mortality (1). Of note, three recent, large cardiovascular outcome trials involving the dipeptidyl peptidase 4 inhibitors saxagliptin (7), alogliptin (8), and sitagliptin (9) failed to demonstrate cardioprotective benefits, and a subset of patients treated with saxagliptin (7) and alogliptin (10) had an increased risk of hospitalization because of heart failure.

In contrast to the effects of vildagliptin, HR increased by 3 to 4 bpm during ID glucose infusion with metformin versus placebo, without any effect on BP. There were predictably only modest falls in SBP and DBP in response to ID glucose, because the majority of patients were normotensive, and none had evidence of autonomic dysfunction. The effect of metformin on HR is consistent with observations of improved left ventricular function (11) and augmented norepinephrine secretion in rodents (12) and may be desirable for preventing postprandial hypotension. It would be of interest to investigate the effects of metformin in patients with type 2 diabetes with postprandial hypotension. It remains to be determined whether the tachycardic effect of metformin is triggered from the gut or by systemic exposure.

Our studies have several limitations. Neither the administration route nor the choice of glucose as a test meal was strictly physiological, but our model circumvented potentially confounding effects of differences in the rate of gastric emptying between individuals. Withdrawal of hypotensive agents for 24 h may not allow a full washout, but this was standardized across study days. We studied acute effects of vildagliptin and metformin, so the effects of chronic exposure are unclear. Finally, our experimental model may have exacerbated the BP-lowering effect of vildagliptin by bypassing gastric distension, which attenuates the postprandial fall in BP (13). Moreover, vildagliptin appears to slow gastric emptying modestly (14), which would also favor attenuation of the fall in SBP.

In summary, vildagliptin lowers BP and elevates HR, whereas metformin increases HR without affecting BP, during ID glucose infusion in patients with type 2 diabetes. These distinct cardiovascular profiles during exposure to enteral nutrients may have implications for postprandial hypotension.

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Author Contributions. T.W. was involved in the conception, design, and coordination of the study; subject recruitment; data collection and interpretation; statistical analysis; and writing of the manuscript. L.G.T., M.J.B., X.Z., and H.W. assisted with data collection and were involved in data interpretation. T.J.L., Z.S., M.H., C.K.R., and K.L.J. were involved in the conception and design of the study and data interpretation. All authors critically reviewed the manuscript and have approved the publication of this final version of the manuscript. T.W., C.K.R., and K.L.J. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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