Chronic Administration of Levosulpiride and Glycemic Control in IDDM Patients With Gastroparesis

PIERLUIGI MELGA, MD
CARLO MANSI, MD
EMANUELA CIUCHI, MD
ROBERTA GIUSTI, MD
LUIGI SCIABÀ, PHD
ROMANO PRANDO, MD

OBJECTIVE — We evaluated the effect of chronic administration of levosulpiride, a prokinetic drug that is a selective antagonist for D_2 dopamine receptors, on the glycemic control of IDDM subjects.

RESEARCH DESIGN AND METHODS — The study was performed on 40 long-standing IDDM subjects with clinical signs of autonomic neuropathy and delayed gastric emptying. Gastric emptying time and glycemic parameters (diurnal glycemic profile and HbA_{1c}) were checked under double-blind conditions before and after the administration of levosulpiride at the dosage of 25 mg t.i.d. orally for 6 months, or placebo.

RESULTS — No significant differences were noted in the glycemic and HbA_{1c} values before and after 6 months of placebo administration. In contrast, after 6 months of levosulpiride, glycemic control had improved (HbA_{1c} 6.7 ± 0.4 and 5.7 ± 0.3%, $P < 0.01$; mean daily glycemia 10.9 ± 0.8 and 8.8 ± 0.4 mmol/l, $P < 0.05$, at the start and at the end of the study), while the dosage of injected insulin (0.65 ± 0.02 IU · kg^{-1} · day^{-1}) and the number of severe hypoglycemic episodes remained unchanged. After 6 months of levosulpiride therapy, the time of gastric emptying was significantly reduced from 321 ± 14 to 261 ± 9 min ($P < 0.001$) and dyspeptic symptoms had improved.

CONCLUSIONS — Our results show the importance of gastric emptying in the maintenance of glycemic control and the usefulness of chronic administration of levosulpiride in diabetic subjects with gastroparesis.

Diabetic gastroparesis develops in ~20–30% of patients with long-standing diabetes and reaches an even higher prevalence (up to 50%) in patients free of dyspeptic symptoms (1,2). Although autonomic neuropathy is likely to be involved (3), several other mechanisms, such as blood glucose concentration, have been suggested in the pathogenesis of gastroparesis. Recent studies have shown that hyperglycemia impairs gastric emptying in both healthy (4) and diabetic subjects (5). On the other hand, in normal subjects, the rate of gastric emptying is a major factor in carbohydrate absorption and thus in blood glucose homeostasis (6,7). Therefore, in diabetic subjects, delayed gastric emptying may contribute to the impairment of glycemic control (5). Whether treatment of diabetic gastroparesis with gastrokinetic drugs results in better control of blood glucose levels is still unresolved.

To elucidate this issue we evaluated the effect of chronic administration of the dopamine receptor antagonist levosulpiride in long-standing IDDM subjects with delayed gastric emptying. Levosulpiride is the levorotatory enantiomer (biologically active form) of sulpiride, a benzamide substitute of established clinical use both in Europe and worldwide (8). The drug stimulates gastrointestinal motility, acting both on pre- and postsynaptic D_2 dopaminergic receptors in the submucosal and myoenteric plexus.

RESEARCH DESIGN AND METHODS

— The study was performed on 40 dyspeptic IDDM outpatients. Details of the patients are reported in Table 1. Insulin therapy consisted of three preprandial injections of regular insulin associated with one or two intermediate insulin preparations. Each patient received a standard hypoglucidic diet with a moderate caloric intake adjusted to age and physical activity. All patients had autonomic neuropathy, assessed according to criteria outlined by Ewing and Clarke (9), and delayed gastric emptying, defined by ultrasound evaluation as final emptying time of 300 min or more. Exclusion criteria, such as organic diseases and contraindications to levosulpiride, have been previously reported (10). Because poor reproducibility of gastric emptying in diabetic patients could be partly ascribed to variations in plasma glucose concentration, all patients entered a 3-month run-in to achieve stable glycemic control. Subsequently patients were randomly assigned to a double-blind 6-month course of oral treatment with placebo (group 1) or levosulpiride (Levopraid, Ravizza Pharmaceutici Spa–BASF Group, Italy) at the dosage of 75 mg/day (group 2) administered 15 min before each of three meals. The total duration of the study was 9 months. In all subjects, circadian glycemic values were evaluated at 3-month intervals during the study: blood samples were taken before and at 1 and 2 h after breakfast, lunch, and dinner (glucose-oxidase method). HbA_{1c} (% of total hemoglobin) was tested by affinity column chromatography (normal range: 2.9–4.6%). All patients kept a record of self-monitored blood glucose, insulin doses, hypoglycemic episodes, and side effects. Every 3 months during the study, each patient was requested to fill in a questionnaire grading the severity of dyspeptic symptoms (10). Gastric emptying was evaluated by ultrasonography on three occasions: on enrollment (to verify eligibility) and before and after treatment. Informed consent was obtained in all cases, and the study was per-

From the Department of Endocrine and Metabolic Sciences (P.M.), the Department of Internal Medicine (C.M., E.C., R.G., R.P.), and the Institute of Pharmacology (L.S.), University of Genoa, Italy.

Address correspondence and reprint requests to Pierluigi Melga, MD, Department of Endocrine and Metabolic Sciences, University of Genoa, Viale Benedetto XV, n. 6, I-16132 Genova, Italy.

Received for publication 29 March 1996 and accepted in revised form 8 August 1996.

Table 1—*Clinical characteristics of the study population*

	Group 1 (placebo)	Group 2 (levosulpiride)
Patients (*n*)	20	20
Sex (M/F)	9/11	8/12
Age (years)	43 ± 2	45 ± 2
Duration of diabetes (years)	21 ± 2	23 ± 2
BMI (kg/m²)	22 ± 1	21 ± 1
CV tests (total score)	3.95 ± 0.3	4.0 ± 0.3

Data are means ± SE. CV tests, cardiovascular tests.

formed in accordance with the principles of the Declaration of Helsinki.

For each subject, the mean of all glycemic values recorded on a given day (mean G) and the difference between the highest and the lowest glycemic values in the day (Δ max G) were calculated and expressed as means ± SE. Differences between groups were analyzed by two-way analysis of variance (among or within subjects) by the Tukey multiple-range test for post hoc comparison. The Mann-Whitney *U* test and Spearman rank-correlation coefficient were used to evaluate symptom scores. Owing to the inter- and intrasubject variability, differences between gastric emptying times were considered significant at 0.01 probability level. $P < 0.05$ was considered significant for metabolic data.

RESULTS — The levosulpiride and placebo groups were similar in terms of clinical characteristics (Table 1). Four patients dropped out for reasons unrelated to treatment. Two levosulpiride-treated patients and one patient on placebo reported minor adverse events, such as breast tenderness, loss of libido, and drowsiness. However, they did not withdraw from the study. Results are reported in Table 2. HbA_{1c} and mean daily glycemic values improved after levosulpiride but not after placebo treatment (Figs. 1 and 2). During the study, the dosage of insulin and the number of hypoglycemic episodes were not significantly different between placebo and levosulpiride-treated patients. The frequency of severe hypoglycemic episodes did not differ between the two groups (Table 2). Levosulpiride significantly improved delayed gastric emptying in comparison with placebo ($P < 0.001$). Levosulpiride, but not placebo, significantly reduced ($P < 0.001$) the symptom score. However, there was no significant correlation between symptom improvement and the changes in gastric emptying induced by levosulpiride ($r_s = 0.12$, $P_2 = 0.72$).

CONCLUSIONS — This study shows that in IDDM subjects with gastroparesis, chronic levosulpiride administration shortens gastric emptying time and significantly improves glycemic control, without any change in insulin dosage or any increase in the number of hypoglycemic episodes. After 3 months of levosulpiride treatment, HbA_{1c} and mean daily glycemic values significantly improved, as compared with placebo, and did not change during the rest of the study. The improvement in glycemic control can be explained by a better synchronization between the onset of action of exogenous insulin and the release of nutrients from the stomach into the intestine and their absorption into the general circulation. Indeed, in diabetic subjects treated with preprandial injections of regular insulin, delayed gastric emptying may cause hypoglycemia 2–3 h after a meal (when the absorption of food is not yet completed), whereas hyperglycemia may occur 4 h or more after a meal when the action of regular insulin decreases. Our data do not conflict with those obtained in NIDDM subjects on high-fiber intake. Indeed, the delayed absorption of glucose, which is related to the delay in gastric emptying induced by fiber, better coincides with insulin release, which is also delayed in these patients (11). Furthermore, our findings are consistent with those of other studies showing that metoclopramide (12) and cisapride (13–16) may improve glycemic control in uncontrolled IDDM with associated gastroparesis. On treating 12 diabetic patients with cisapride for 12 months, Champion et al. (13) found a significant improvement in the HbA_{1c} values and fewer episodes of hypoglycemia.

The gastrokinetic effect of levosulpiride in diabetic subjects has been demonstrated both after single (17) and repeated (1

Table 2—*Studied parameters at inclusion (−3), before (0), during (+3), and after (+6) treatment with placebo (group 1) and levosulpiride (group 2)*

	Time (months)							
	−3		0		+3		+6	
Group	1	2	1	2	1	2	1	2
Gastric emptying time (min)	321 ± 14	327 ± 14	327 ± 12	321 ± 14	—	—	318 ± 12	261 ± 9§
Dyspeptic symptoms (total score)	14 ± 3	13 ± 3	13 ± 3	13 ± 3	12 ± 3	8 ± 2‡	11 ± 3	6 ± 2§
Insulin dose (IU · kg^{-1} · day^{-1})	0.58 ± 0.02	0.59 ± 0.02	0.64 ± 0.02	0.65 ± 0.02	0.65 ± 0.02	0.66 ± 0.02	0.66 ± 0.02	0.64 ± 0.02
HbA_{1c} (%)	6.6 ± 0.4	6.7 ± 0.4	6.6 ± 0.4	6.7 ± 0.4	6.6 ± 0.3	6.1± 0.3†	6.8 ± 0.2	5.7 ± 0.3†
Mean G (mmol/l)	10.7 ± 0.7	10.8±0.7	10.6 ± 0.7	10.9 ± 0.8	10.8 ± 0.7	9.2 ± 0.5*	10.6 ± 0.7	8.8 ± 0.4*
Δ max G (mmol/l)	6.0 ± 0.4	6.1 ± 0.4	5.5 ± 0.4	5.7 ± 0.4	5.3 ± 0.4	3.5 ± 0.3†	5.2 ± 0.4	3.5 ± 0.3†
Hypoglycemic events (*n*/year)	2.0 ± 0.1	1.9 ± 0.1	1.5 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	1.7 ± 0.1

Data are means ± SE. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.005$, §$P < 0.001$ compared with time 0 and with group 1.

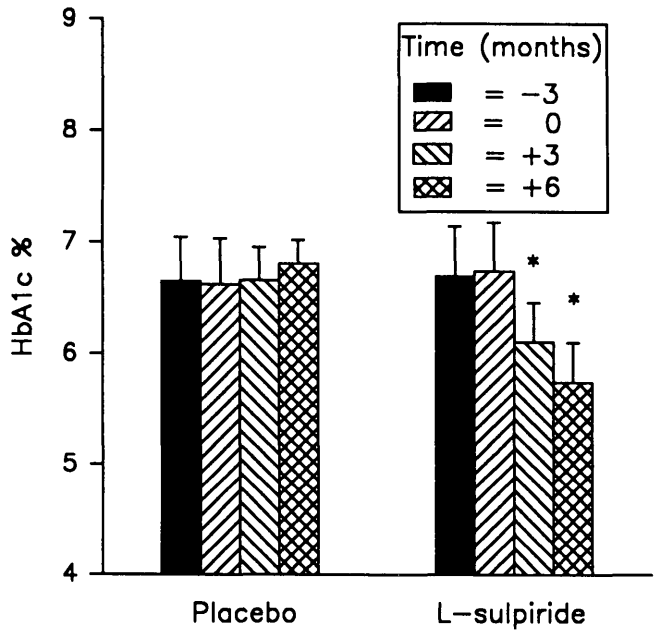

Figure 1—*HbA_{1c} values (%) in the two groups of diabetic subjects before and after placebo (group 1) or levosulpiride (group 2) administration. *P < 0.01 vs. 0 and vs. placebo.*

month) administration (10). We have now shown that the effect on gastric emptying time is maintained when treatment is prolonged for 6 months, and there is no reason to exclude, on the basis of the present and previous studies (10,17), that the effect may have already been found after 3 months of treatment. The improvement in mean daily glycemic values and in HbA_{1c} after 3 months of levosulpiride treatment indirectly supports this assumption, if one accepts that the glycemic control obtained at the end of the study is at least partly influenced by gastric emptying. The antagonism of levosulpiride on dopamine receptors may be a relevant component of its effect because an increase in dopaminergic activity has been reported in diabetes (18).

In conclusion, our results support the role of gastric emptying in maintaining glycemic control in IDDM subjects. These findings have relevance to the management of these patients and suggest that diabetic patients with unexplained poor glycemic control should be investigated for gastric emptying abnormalities. Levosulpiride may constitute a safe therapeutic option for the chronic treatment of diabetic patients with dyspeptic symptoms and/or delayed gastric emptying.

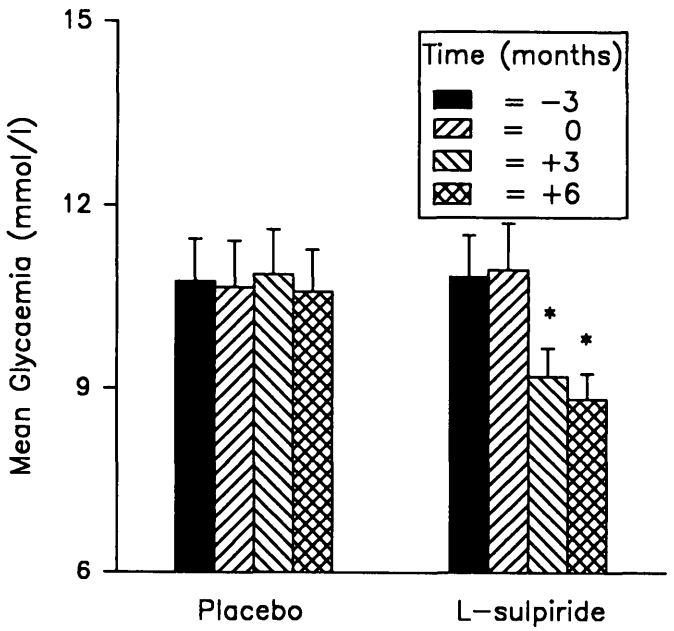

Figure 2—*Mean daily glycemia (mmol/l) in the two groups of diabetic subjects before and after placebo (group 1) or levosulpiride (group 2) administration. *P < 0.05 vs. 0 and vs. placebo.*

References

1. Keshavarzian A, Iber FL, Vaeth J: Gastric emptying in patients with insulin-requiring diabetes mellitus. *Am J Gastroenterol* 82:29–35, 1987
2. Horowitz M, Fraser R: Disordered gastric motor function in diabetes mellitus. *Diabetologia* 37:543–551, 1994
3. Clarke BF, Ewing DJ, Campbell JW: Diabetic autonomic neuropathy. *Diabetologia* 17:195–212, 1979
4. Oster-Jorgensen E, Pedersen SA, Larsen ML: The influence of induced hyperglycaemia on gastric emptying in healthy humans. *Scand J Clin Lab Invest* 50:831–836, 1990
5. Fraser R, Horowitz M, Maddox AF, Harding PE, Chatterton BE, Dent J: Hyperglycaemia slows gastric emptying in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30:675–680, 1990
6. Horowitz M, Edelbroek MAL, Wishart JM, Straathof JW: Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. *Diabetologia* 36:857–862, 1993
7. Mourot J, Thouvenot P, Couet C, Antoine JM, Krobikca A, Debry G: Relationship between the rate of gastric emptying and glucose and insulin responses to starchy foods in young healthy adults. *Am J Clin Nutr* 48:1035–1040, 1988
8. Rossi F, Forgione A: Pharmacotoxicological aspects of levosulpiride. *Pharmacol Res* 31:81–94, 1995
9. Ewing DJ, Clarke BF: Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 285:916–918, 1982
10. Mansi C, Savarino V, Vigneri S, Perilli D, Melga P, Sciabà L, De Martini D, Mela GS: Gastrokinetic effects of levosulpiride in dyspeptic patients with diabetic gastroparesis. *Am J Gastroenterol* 90:1989–1993, 1995
11. Torsdottir I, Alpsten M, Holm G, Sandberg AS, Tolli J: A small dose of soluble alginate-fiber affects postprandial glycaemia and gastric emptying in humans with diabetes. *J Nutr* 121:795–799, 1991
12. Muls EE, Lamberigts GF: Uncontrolled diabetes mellitus due to gastroparesis diabeticorum: treatment with metoclopramide. *Postgrad Med J* 57:185–188, 1981

13. Champion MC, Gulenchyn K, Braaten J: Cisapride is effective in the management of diabetic gastroparesis. *J Gastroenterol Hepatol* 5 (Suppl.):25, 1990
14. Montoya ML, Hebuterne X, Carriere D, Rampal P: Effect of cisapride on small intestinal motor activity in insulin-dependent diabetics (Abstract). *Gastroenterology* 100:A471, 1991
15. Wiseman LR, Faulds D: Cisapride: an updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. *Drug* 47:116–152, 1994
16. Horowitz M, Maddox A, Harding PE, Maddern GJ, Chatterton BE, Wishart J, Shearman DJC: Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastronterology* 92:1899–1907, 1987
17. Arienti V, Boriani L, Sorrenti G, Califano G, Sama MG, Gasbarrini G: Ultrasonographic assessment of gastric and gallbladder emptying in patients with long-standing type 1 and type 2 diabetes mellitus: effect of a single oral dose of levosulpiride (Abstract). *Gastroenterology* 110 (Suppl.):A624, 1996
18. Lozovsky D, Saller CF, Kopin IJ: Dopamine receptor binding is increased in diabetic rats. *Science* 214:1031–1032, 1981