In the study recently reported by Chiasson et al. (1), it was concluded that miglitol, a pseudomonosaccharide α-glucosidase inhibitor, can be combined effectively with metformin therapy to give significantly greater reductions in HbA1c and postprandial plasma glucose levels than metformin alone in middle-aged patients in whom type 2 diabetes is insufficiently controlled by diet alone. The combined therapy had a good safety profile, with only a trend toward an increase in the number of gastrointestinal side-effects due to miglitol acting at the small intestine by delaying the digestion of complex carbohydrates (2).

The absorption of metformin occurs mainly in the small intestine, and it has been shown that high concentrations of the compound (10-100 times plasma levels) accumulate in the walls of the gastrointestinal tract (rev. in 3). Therefore, possible pharmacokinetic interference with drugs acting on the intestinal wall are not excluded. We previously demonstrated in six healthy subjects that acarbose (100 mg), a pseudotetrasaccharide that is currently the leading α-glucosidase inhibitor on the market, induces significant reductions in early (90-, 120-, and 180-min) serum levels, peak concentrations (C_{max} 1.22 ± 0.14 vs. 1.87 ± 0.60 mg/l; P < 0.05), and area under the curve for 0-540 min (AUC_{0-540 min}; 423 ± 55 vs. 652 ± 55 mg • min • 1^{-1}; P < 0.05) of metformin ingested as two tablets of 500 mg with a standardized breakfast (4).

To our knowledge, such interference of miglitol on the pharmacokinetics of metformin has not yet been studied. However, although our group did not observe any significant alteration of the glibenclamide pharmacokinetics in acarbose-treated type 2 diabetic patients (5), we observed slight modifications of the pharmacokinetic parameters of glibenclamide after ingestion of miglitol in six healthy volunteers (unpublished data). In a double-blind crossover trial, each subject was randomly allocated during two consecutive 7-day periods to either miglitol (3 X 50 mg during the first 3 days and 3 X 100 mg/day during the last 4 days) or placebo. At the 7th and 14th day of the study, the overnight-fasted subjects ingested 5 mg glibenclamide with the first bite of a standardized breakfast together with either 100 mg miglitol or placebo. Venous blood samples were taken from 0 to 540 min to measure serum glibenclamide concentrations by radioimmunoassay. Time-to-peak (T_{max}; 215 ± 40 vs. 230 ± 24 min; NS) and peak serum glibenclamide levels (C_{max}; 190 ± 33 vs. 225 ± 31 µg/l; NS) were similar after miglitol and placebo, respectively. However, the glibenclamide AUC_{0-540 min} was significantly lower after miglitol than after placebo (40,358 ± 3,203 vs. 59,950 ± 9,193 µg • min • 1^{-1}; P< 0.05).

These observations in normal subjects suggest that a potential interference of miglitol on the pharmacokinetics of metformin cannot be excluded during combined therapy in type 2 diabetic patients. Whether this interference exists and to what extent it may influence the efficacy and/or safety of such a combined therapy remains to be investigated.

References