

The Effect of Timing on Gliclazide Absorption and Action

Fukashi ISHIBASHI and Seiryō TAKASHINA

Department of Internal Medicine, Hiroshima General Hospital, 1-3-3, Jigozen, Hatsukaichi, Hiroshima, 738, Japan

ABSTRACT

In this study we tried to determine when in relation to meals gliclazide should be taken for optimum hypoglycemic action. Eight non-insulin-dependent diabetics participated in this study during hospitalization for glycemic control.

After stabilization of glycemic control on gliclazide, they took a 40 mg tablet of gliclazide either 30 minutes before, immediately before, or immediately after breakfast on 3 consecutive days. We then determined serum gliclazide, glucose and IRI levels at 30-minute intervals beginning 30 minutes before breakfast and continuing until 2 hours after breakfast.

Gliclazide taken 30 minutes before breakfast increased in serum concentration before the meal-induced hyperglycemia, but that taken just before or just after breakfast was poorly absorbed and showed smaller and greatly delayed peaks. When taken 30 minutes before breakfast, gliclazide produced a peak of IRI 30 minutes after the meal; taken immediately before or after, it took twice to three times as long to produce an IRI peak. Postprandial hyperglycemia remained pronounced for a relatively long time when the drug was taken immediately before or after the meal.

Based upon the experimental evidence we propose the tentative recommendation that gliclazide is best taken 30 minutes before breakfast.

Key words: *Gliclazide, Pharmacokinetics, Influence of food*

We know very little about the best time to take oral hypoglycemic agents. The usual advice to take them after meal, rather than before, is meant to avoid hypoglycemia. However, the new agent glipizide exerts its full hypoglycemic action only if administered 30 minutes before eating.

Gliclazide, a newly developed sulfonylurea²⁾, is to be taken before meals. Its serum concentrations have been studied when orally administered in healthy subjects³⁾ and in diabetics⁶⁾, but never in relation to meals.

We describe in this paper how timing with respect to meals affects the absorption and action of this drug in diabetics.

MATERIALS AND METHODS

Eight NIDDM diabetics (5 male, 3 female, aged 34-67 years, body mass index 21.4-24.0), hospitalized for glycemic control, participated in this study. Their fasting plasma glucose (FPG) before admission ranged from 212 to 164 mg/dl. None had diabetic microangiopathy or any renal or digestive disease which would disturb drug metabolism or excretion. After these patients had been stabilized with gliclazide (their FPG ranging from 86 mg/dl to 102 mg/dl and peak plasma glucose after breakfast less than 200 mg/dl), they randomly assigned

40 mg tablets of the drug to take 30 minutes before, immediately before, or immediately after breakfast on three consecutive days. Every day, they took identical isocaloric, typical Japanese breakfast (492 kcal), containing 77 g of carbohydrate, 24.5 g of protein, and 13.5 g of fat. We drew blood regularly every 30 minutes, beginning 30 minutes before breakfast until 2 hours after breakfast. Serum or plasma was separated and kept at -20 °C until use. Plasma glucose was determined by the glucose oxidase method. Serum IRI was measured by radioimmunoassay using a commercial human insulin RIA kit (Insulin Eiken, Tokyo). Serum gliclazide was assayed with high performance liquid chromatography⁵⁾. 40 mg tablets of gliclazide were provided by Dainippon Phar. Co. (Osaka, Japan).

Statistical analysis was carried out using paired t-tests.

RESULTS

Diabetics who took gliclazide 30 minutes before breakfast experienced peak serum levels 60 minutes after breakfast. The other subjects experienced later and lower peaks; gliclazide taken immediately after breakfast (10 minutes after beginning breakfast) caused a significant rise in serum levels

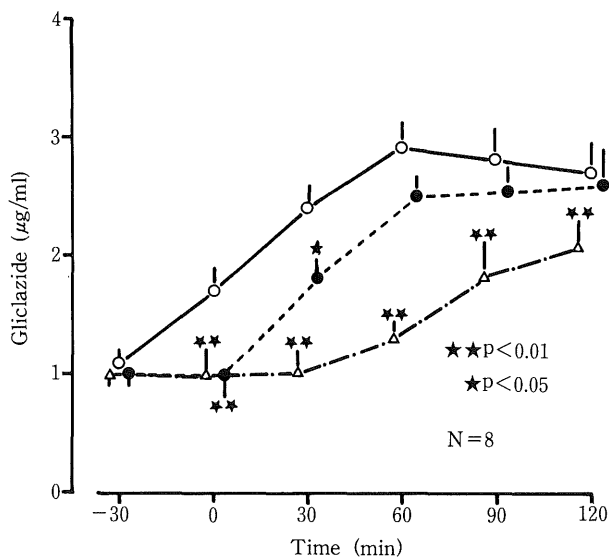


Fig. 1. Influence of timing of gliclazide administration on its serum concentration in NIDDM. After achieving glycemic control with glyclazide, subjects took a 40 mg tablet of gliclazide 30 minutes before breakfast (○—○), immediately before (●—●), or immediately after breakfast (△—△) on 3 consecutive days. The first method produced significantly different results than the other two.

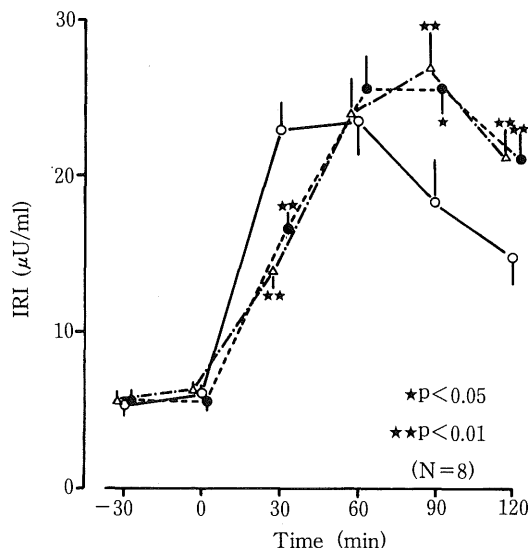


Fig. 2. Influence of timing of gliclazide administration on meal-induced IRI response in NIDDM. After achieving glycemic control, subjects took a 40 mg tablet of gliclazide 30 minutes before breakfast (○—○), immediately before (●—●), or immediately after breakfast (△—△) on 3 consecutive days. The first method produced significantly different results than the other two.

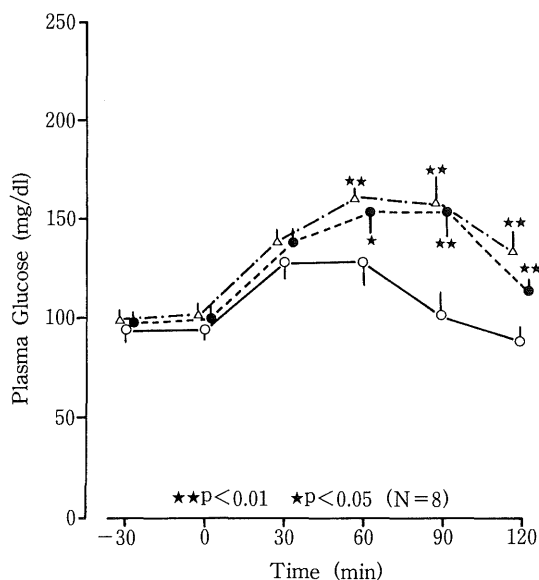


Fig. 3. Influence of timing of gliclazide administration on postprandial hyperglycemia in NIDDM. After achieving glycemic control, subjects took 40 mg tablet of gliclazide 30 minutes before breakfast (○—○), immediately before (●—●), or immediately after breakfast (△—△) on 3 consecutive days. The first method produced significantly different results than the other two.

only after 90 minutes (Fig. 1).

Diabetics who took gliclazide 30 minutes before breakfast displayed submaximal IRI levels 30 minutes after eating and no measurable IRI increase before eating. Those who took the drug after eating had still not experienced their peak IRI

level 120 minutes after breakfast (Fig. 2).

Diabetics who took gliclazide 30 minutes before breakfast also had less postprandial hyperglycemia for less time than did the other subjects. Their serum glucose did not fall at all before breakfast began (Fig. 3).

DISCUSSION

Gliclazide¹⁾ is absorbed rapidly and acts rapidly, but can be delayed in both respects by food intake⁹⁾. Glibenclamide also has a stronger action when taken before breakfast⁷⁾.

Gliclazide has been widely used because of its expected suppression of platelet adhesiveness and coagulation⁴⁾. Its serum concentration when orally administered in healthy subjects³⁾ and in diabetics^{6,8)} has been previously studied. All these subjects, however, were in the fasting state. One study reported that administration after breakfast impairs the absorption and action of this drug¹⁰⁾.

Given the importance of strict glycemic control in preventing diabetic microangiopathy we were to study the pharmacokinetics of gliclazide with respect to meals. The delay in absorption, the delay in IRI response, and the more severe postprandial hyperglycemia experienced by those who took gliclazide immediately before or after breakfast under experimental conditions, together with the lack of blood glucose decline among those who took the drug 30 minutes before breakfast, lead us to recommend that patients take gliclazide 30 minutes before the meal in order to suppress postprandial hyperglycemia.

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