Slow Elimination of Glyburide in NIDDM Subjects

ANDERS JÖNSSON, MD
TONY RYDBERG, MSC PHARM
GÖRAN EKBERG, MD
BENGT HALLENGREN, MD, PHD
ARNE MELANDER, MD, PHD

OBJECTIVE — To determine the terminal elimination half-life of glyburide in non-insulin-dependent diabetes mellitus (NIDDM) subjects after cessation of long-term treatment.

RESEARCH DESIGN AND METHODS — Ten NIDDM patients (5 of each sex, 36–72 years old, without hepatic or renal disease) taking a median glyburide dose of 14 mg/day, who were to start insulin therapy because of sulfonylurea failure, were studied. Serum glyburide concentrations, measured by a newly developed selective and sensitive liquid chromatographic method, were followed from 10 to 48 h after the last glyburide dose.

RESULTS — Serum glyburide levels declined in three different phases, with a terminal γ-phase between 18 and 48 h having a mean ± SD half-life of 15.0 ± 6.7 h. Two patients had half-lives over 20 h. The half-life values did not correlate with fasting blood glucose, age, body weight, body mass index, or creatinine levels. The latter agrees with the assumption that glyburide is completely eliminated by metabolic transformation. Although longer than previously observed, the current half-life values are in accordance with clinical experience that glyburide is a long-acting sulfonylurea.

CONCLUSIONS — The elimination of glyburide in NIDDM subjects is slower than previously reported. The long half-life adds support to the use of a once-daily dosage of glyburide. It also justifies increased caution when using this sulfonylurea.

The second-generation sulfonylurea glyburide is commonly used. It is long-acting (1) and has provoked numerous long-lasting hypoglycemic reactions, which have sometimes been fatal (2–4). In spite of this, its elimination half-life is allegedly short, about 1–5 h in some (5–7) and up to 10 h in other studies (8,9). However, some of these studies were conducted in nondiabetic individuals, others by single dose, and the serum concentrations of glyburide were sometimes followed for only 6–12 h. A selective liquid chromatographic method with high sensitivity was developed recently, allowing measurements of very low glyburide levels (10). The aim of this study was to assess the terminal elimination half-life of glyburide in non-insulin-dependent diabetes mellitus (NIDDM) subjects after cessation of long-term glyburide therapy because of sulfonylurea failure.

RESEARCH DESIGN AND METHODS

Ten Caucasian NIDDM patients (5 of each sex) who were to start insulin therapy because of sulfonylurea failure were studied. They were recruited consecutively from the diabetes outpatient clinic at Malmö General Hospital. Expressed by median and range their age was 56 years (36–72 years), duration of NIDDM was 10.5 years (1–18), body mass index (BMI) was 25.4 kg/m^2 (21.6–31.0 kg/m^2), HbA_{1c} was 10.8% (9.5–13.2%; reference value <5.7%), and duration of glyburide therapy was 6 years (2 months–10 years). Three patients had a daily dose of 10.5 mg, and 7 patients took 14 mg per day in divided doses. Four patients were treated with metformin, which was withdrawn the day before the study was started. All other medication (Table 1) was unchanged during the study, and patients were asked not to change their alcohol and smoking habits during the study. No patient had clinical signs or symptoms of renal or hepatic disease, and serum creatinine and liver enzyme levels were normal in each case. Microalbuminuria (30–300 mg/day) was found in 5 patients. Informed consent was obtained from each patient, and the study was approved by the Lund University Medical Faculty Ethics Committee.

All patients were studied and fed at the metabolic ward of the Department of Endocrinology, Malmö General Hospital, but they slept at home. On the first day, patients arrived in the ward at 0700 after fasting at least 10 h. Patients then

From the Departments of Endocrinology, Clinical Pharmacology, and Community Health Sciences, Lund University, Malmö General Hospital, Malmö; and the Hospital Pharmacy, Kristianstad County Central Hospital, Kristianstad, Sweden.

Address correspondence and reprint requests to Anders Jönsson, MD, Department of Endocrinology, Malmö General Hospital, S-214 01 Malmö, Sweden.

Received for publication 11 May 1993 and accepted in revised form 9 September 1993.

NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index.

Table 1—*Patient medication in addition to glyburide*

Patient no.	Age (years)	Medication
1	58	Metformin, furosemide, enalaprilate
2	39	Procyclidine, perphenazine
3	36	None
4	69	Metformin, nifedipine, aspirin, atenolol
5	72	Metformin, furosemide, digoxin, amiloride
6	53	Pancreatic enzymes
7	60	Metformin
8	48	Furosemide, enalaprilate
9	59	Furosemide, melperone, verapamil, amiloride, nitroglycerine, terbutaline
10	42	Clofibrate

took their ordinary glyburide doses 30 min before breakfast (which was served at 0800) and lunch (1200), but the last glyburide dose, normally taken at 1700, before dinner, was delayed until 2200. Insulin therapy started in the morning of day 2.

Venous blood samples were taken at 0715 and 0730 (0 samples = minimum steady-state levels) and then at 0800, 0815, 0830, 0930, 1030, and 1130 on day 1; and at 10, 12, 14, 16, 18, 20, and 22 h after the last glyburide dose on day 2. On day 3, samples were taken twice (36 and 43–48 h after the last dose), and a final (serum blank) sample was taken on either day 6, 7, or 8. Analyses verified that all serum blanks contained no detectable amounts of glyburide. Blood samples were collected in plain 10-ml tubes; serum was separated by centrifugation and kept frozen at −20°C until analyzed. Aliquots from the blank samples of each subject were used to prepare standard curves. The serum concentrations of glyburide were measured by a newly described liquid chromatographic method (10). Its minimum detectable concentration is 1 ng/ml, and its precision at this level expressed as relative SD is 8.9%. Each subject's elimination rate constant (k) was calculated by the least-squares method, and half-lives were expressed as $t_{1/2} = (\ln 2)/k$. Data are expressed as means ± SD.

RESULTS — As seen in Fig. 1 and Table 2, mean serum glyburide levels appeared to decline in three different phases, an early (α) phase, which was not calculated, a subsequent (β) phase between 10 and 18 h with a mean half-life of 5.4 h, and a terminal (γ) phase between 18 and 48 h with a mean half-life of 15 h. One subject had a terminal half-life of 26.9 h and another 22.9 h. In 2 patients, interfering peaks in their chromatograms precluded measurements of glyburide after 18 (pat. no. 6) and 22 (pat. no. 9) h. Hence the terminal (γ) phase was determined in the remaining 8 patients, and their concentrations at 36 h after the last dose were 2.3–8.1 ng/ml. Four of these patients had measurable serum glyburide levels even at 48 h after the last dose ranging between 1.4 and 4.5 ng/ml. No correlation was found between terminal glyburide half-life values, on the one hand, and the fasting blood glucose, body weight, BMI, creatinine, or age, on the other. The minimum steady-state concentrations (before the morning dose, with a dose-free interval of at least 14.5 h) ranged from 9 to 166 ng/ml (38 ± 46 ng/ml).

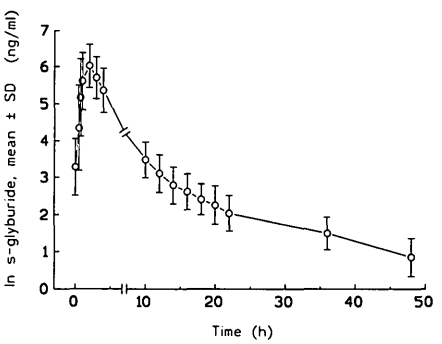

Figure 1—*Elimination of glyburide (means ± SD) in 10 NIDDM subjects after cessation of glyburide therapy because of secondary failure. Note the increasing slopes with time.*

CONCLUSIONS — These findings show that the elimination of glyburide in NIDDM subjects during therapeutic conditions is slower than reported previously. However, a long half-life is in keeping with clinical experience that glyburide is a long-acting sulfonylurea, and it also helps to explain why glyburide sometimes may provoke long-lasting hypoglycemic reactions (2–4). A long elimination half-life has been reported previously (11,12), although with nonspecific assays. The method used in this study completely separates glyburide from its metabolites (10).

It might be argued that the long half-life was attributable to the fact that all patients had secondary sulfonylurea failure. However, one might then expect the half-lives to increase with the fasting blood glucose levels, but there was no such relation. In fact, the patient with the next-longest half-life (22.9 h) had the lowest fasting blood glucose (9.0 mM), and the patient with the longest half-life (26.9 h) had a rather low fasting blood glucose (11.1 mM). Moreover, no correlations were found between glyburide half-life and creatinine, body weight, BMI, or age. This confirms that the elimination of glyburide is mainly independent of renal function (compare 7) and also suggests that it is independent of body composition and (other) age-related changes.

It could also be argued that the slow elimination of glyburide in these patients was attributable to interactions with other medication. However, except

Table 2—*Patient characteristics and glyburide elimination half-lives*

Patient no.	Age (years)	Sex	Fasting blood glucose (mM)	Body weight (kg)	BMI (kg/m^2)	Serum creatinine (μM)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)
1	58	F	9.0	77	29.7	91	5.6	22.9
2	39	M	10.7	88	31.0	89	4.5	9.6
3	36	F	13.2	58	23.7	80	7.6	15.1
4	69	F	12.6	68	25.1	76	6.7	13.1
5	72	M	12.9	77	26.6	73	7.1	14.4
6	53	M	10.2	67	21.6	79	5.9	—
7	60	F	10.4	54	24.0	63	4.8	26.9
8	48	F	15.5	74	25.6	90	5.4	10.6
9	59	M	19.9	78	29.0	103	3.0	—
10	42	M	14.7	78	25.1	72	3.7	7.6

for aspirin (patient no. 4), none of the given drugs is known to interfere with glyburide kinetics. In addition, most NIDDM patients are treated with other drugs, particularly cardiovascular agents. Furthermore, the patient with the longest half-life (patient no. 7) of glyburide had no other treatment than metformin, which is rapidly eliminated, unchanged by renal excretion, and was withdrawn the day before the study was started.

The minimum steady-state concentrations of glyburide varied extensively as observed previously using a nonspecific method (13). With one possible exception, however, all patients had minimum steady-state concentrations at or above the assumed effective level (14). In addition, recent studies indicate that the minimum effective serum concentration of glyburide may be much lower than previously assumed (14,15). Moreover, the slow terminal elimination phase may be an expression of glyburide binding in a deep compartment, including the target cells; indeed, glyburide seems unique among sulfonylureas in that it may accumulate within β-cells (16). Accordingly, the slow terminal elimination of glyburide would be clinically relevant. Note also that the current study was conducted with the micronized formulation of glyburide, whereas the formulation used in the U.S. is a nonmicronized formulation that is more slowly absorbed than the micronized one (17). This slow absorption might further prolong the elimination of glyburide.

To summarize, glyburide is more slowly eliminated than previously reported. The long half-life adds support to the use of a once-daily dosage of glyburide. It also justifies increased caution when using this sulfonylurea.

Acknowledgments— This study was supported by a grant from Apoteksbolaget's (The Swedish Corporation of Pharmacies) Fund for Research and Studies in Health Economics and Social Pharmacy, by an educational grant from Apoteksbolaget, and by a fund of the Swedish Academy of Pharmaceutical Sciences (Apotekens Kontrollaboratoriums Stipendiefond). The skillful technical assistance of Mona Svärd-Hansson is gratefully acknowledged.

References

1. Gerich JE: Oral hypoglycemic agents. *N Engl J Med* 321:1231–45, 1989
2. Berger W, Caduff F, Pasquel M, Rump A: Slow elimination of glibenclamide in NIDDM subjects (in German). *Schweiz Med Wschr* 116:145–51, 1986
3. Asplund K, Wiholm BE, Lithner F: Glibenclamide-associated hypoglycemia: a report on 57 cases. *Diabetologia* 24:412–17, 1983
4. Seltzer HS: Drug-induced hypoglycemia. *Endocrinol Metab Clin N Am* 18:163–83, 1989
5. Rogers HJ, Spector RG, Morrison PJ, Bradbrook ID: Pharmacokinetics of intravenous glibenclamide investigated by a high-performance liquid chromatographic assay. *Diabetologia* 23:37–40, 1982
6. Matsuda A, Kuzuya T, Sugita Y, Kawashima K: Plasma levels of glibenclamide in diabetic patients during its routine clinical administration determined by a specific radioimmunosassay. *Horm Metab Res* 15:425–28, 1983
7. Pearson JG, Antal EJ, Raehl CL, Gorsch HL, Craig WA, Albert KS, Welling PG: Pharmacokinetic disposition of [^{14}C]glyburide in patients with varying renal function. *Clin Pharmacol Ther* 39:318–24, 1986
8. Schwinghammer TL, Antal EJ, Kubacka RT, Hackimer ME, Johnston JM: Pharmacokinetics and pharmacodynamics of glyburide in young and elderly nondiabetic adults. *Clin Pharmacy* 10:532–38, 1991
9. Coppack SW, Lant AF, McIntosh CS, Rodgers AV: Pharmacokinetic and pharmacodynamic studies of glibenclamide in non-insulin dependent-diabetes mellitus. *Br J Clin Pharmacol* 29:673–84, 1990
10. Rydberg T, Wåhlin-Boll E, Melander A: Determination of glibenclamide and its

two major metabolites in human serum and urine by column liquid chromatography. *J Chromatogr* 564:223–33, 1991
11. Behrle M: *Untersuchungen zur pharmakokinetik von glibenclamid bei nierengesunden und niereninsuffizienten diabetikern*. PhD thesis. Heidelberg, Germany, Ruprecht-Karl-Universität, 1980
12. Balant L, Fabre J, Zahnd GR: Comparison of the pharmacokinetics of glipizide and glibenclamide in man. *Eur J Clin Pharmacol* 8:63–69, 1975
13. Sartor G, Melander A, Scherstén B, Wåhlin-Boll E: Serum glibenclamide in diabetic patients and influence of food on the kinetics and effect of glibenclamide. *Diabetologia* 18:17–22, 1980
14. Groop LC, Barzilai N, Ratheiser K, Luzi L, Wåhlin-Boll E, Melander A, DeFronzo RA: Dose-dependent effects of glyburide on insulin secretion and glucose uptake in humans. *Diabetes Care* 14:724–27, 1991
15. Melander A, Bitzén P-O, Faber O, Groop L: Sulfonylurea antidiabetic drugs: an update of their clinical pharmacology and rational therapeutic use. *Drugs* 37: 58–72, 1989
16. Hellman B, Sehlin J, Täljedal IB: Glibenclamide is exceptional among hypoglycemic sulfonylureas in accumulating progressively in β-cell-rich pancreatic islets. *Acta Endocrinol* 105:385–90, 1984
17. Arnqvist HJ, Karlberg BE, Melander A: Pharmacokinetics and effects of glibenclamide in two formulations, HB 419 and HB 420, in type 2 diabetes. *Annals Clin Res* 15 (Suppl. 37):21–25, 1983