

Transfer of Glyburide and Glipizide Into Breast Milk

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OBJECTIVE — To determine if glyburide and glipizide are excreted into breast milk and if breast-feeding from women taking these drugs causes infant hypoglycemia.

RESEARCH DESIGN AND METHODS — We studied eight women who had received a single oral dose of 5 or 10 mg glyburide. Drug concentrations were measured in maternal blood and milk for 8 h after the dose. In a separate study, five women were given a daily dosage (5 mg/day) of glyburide or glipizide, starting on the first postpartum day. Maternal blood and milk drug concentrations and infant blood glucose were measured 5–16 days after delivery.

RESULTS — In the single-dose glyburide study, the mean maximum theoretical infant dose (MTID) as a percent of the weight-adjusted maternal dose (WAMD) was <1.5 and <0.7% for the 5- and 10-mg doses, respectively. For the five women taking daily dosages, the mean MTID as a percent of the WAMD was <28% for glyburide and <27% for glipizide. The high estimates were due to the insensitivity of the assay. Neither glyburide nor glipizide were detected in breast milk in either study and blood glucose was normal in the three infants (one glyburide and two glipizide) who were wholly breast-fed when the drug concentrations were at steady state.

CONCLUSIONS — Neither glyburide nor glipizide were detected in breast milk, and hypoglycemia was not observed in the three nursing infants. Both agents, at the doses tested, appear to be compatible with breast-feeding.

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The prevalence of type 2 diabetes is rising dramatically worldwide. There are currently 110 million people with diabetes, and this number is expected to double by the year 2010 (1). In the U.S., Canada, and Europe, over 80% of diabetes cases are type 2 (2). Although previously considered a disease of elderly

people, there has been an increasing incidence of type 2 diabetes in younger individuals, including women in their reproductive years (3,4). Many of these women are taking oral hypoglycemic agents before conception for glycemic control. The current standard of treatment is to change these women's medica-

tions to insulin before conception (if pregnancy is planned) and continue its use during pregnancy and into the postpartum period if patients are breast-feeding (5). This approach aims to prevent fetal and neonatal hypoglycemia secondary to oral hypoglycemic agents, as insulin does not cross into either the fetal compartment or milk at usual doses. However, many women are anxious to return to oral hypoglycemic agents immediately after giving birth because of the cumbersome and painful administration of insulin. Moreover, in many parts of the world, injectable insulin is not available due to its prohibitive cost. The ease of administration and effectiveness of glyburide or glipizide would make either drug ideal for women with type 2 diabetes who are breast-feeding. However, data are lacking about the safety of such treatment for nursing infants.

The objective of both studies was to determine if glyburide and glipizide were excreted into breast milk. The second objective of the daily-dose study was to determine if breast-feeding from women treated with these drugs caused infant hypoglycemia.

RESEARCH DESIGN AND METHODS

The single-dose protocol was approved by the University of Toronto Internal Review Board and the Mount Sinai Hospital Board of Ethics (Toronto, Canada). The daily-dose protocol was approved by the Memorial Health Service Research Council (Long Beach, CA) and the Committee on Human Research (University of California, San Francisco). The two studies were conducted independently of each other. A written informed consent was obtained from all participants.

The study cohorts included women with type 2 diabetes who had recently delivered at Mount Sinai Hospital (Toronto, Canada) or the Women's Pavilion, Miller Children's Hospital (Long Beach, CA) and who were currently breast-feeding. In Toronto, the women used insulin during pregnancy and continued using insulin in the postpartum period. In Long Beach, all study subjects were treated with insulin

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Abbreviations: HPLC, high-performance liquid chromatography; MTID, maximum theoretical infant dose; WAMD, weight-adjusted maternal dose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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during their pregnancy and were changed to nonmicronized glyburide (5 mg/day) or immediate-release glipizide (5 mg/day) immediately after delivery by their personal physicians independently of the study.

In Toronto, patients were excluded if they had known type 1 or gestational diabetes. Also excluded were patients with severe hepatic or renal dysfunction; with adrenal or pituitary insufficiency; with a history of drug and/or alcohol abuse; using steroids, thiazides, antibiotics, or β -blockers; or with any condition that would affect lactation.

In Long Beach, subjects were eligible for the study if they had been delivered by cesarean section and were in the immediate postoperative period, had type 2 diabetes that could not be controlled by diet alone, and had a pediatrician assigned to their newborn infant. Women were excluded from enrollment if the gestational age at delivery was <37 weeks; the infant had intrauterine growth retardation (weight <10th percentile for gestational age); the infant developed hypoglycemia (blood glucose <40 mg/dl) within 24 h of birth or any other condition, such as sepsis, polycythemia, severe hyperbilirubinemia, or failure to thrive; the infant had a major birth defect; or the infant did not have a pediatrician assigned for routine follow-up care.

Single-dose study (Toronto)

A single 5-mg dose of glyburide was given to six mothers (subjects 1–6), and a single 10-mg dose was given to two mothers (subjects 7 and 8). A venous blood sample was drawn at 2, 4, 6, and 8 h after the dose of glyburide. At the same time points, 5 ml of breast milk were also expressed and collected using an electric breast pump. Capillary glucose measurements were also conducted every 2 h until the study was completed. Women were given breakfast after the dose of glyburide to prevent hypoglycemia. They resumed their usual insulin regimen either before lunch if the capillary glucose was ≥ 8 mmol/l (144 mg/dl) or before dinner. Women were asked to refrain from breast-feeding for 12 h after the glyburide dose was given. During these 12 h, infants were fed formula or breast milk pumped by their mother before the day of the study. The maximum theoretical infant dose (MTID; milligrams per kilogram per day) was calculated using the detection

limit (0.005 $\mu\text{g/ml}$) and an estimated daily milk consumption of 150 ml/kg. This dose was then divided by the maternal dose (milligrams per kilogram per day), and the result was multiplied by 100 to obtain the MTID as a percent of the weight-adjusted maternal dose (WAMD).

Daily-dose study (Long Beach)

Over a 2-year period, all women who met the study's criteria were enrolled in the study. Of the initial enrollees, five (two on glyburide and three on glipizide) did not breast-feed for reasons unrelated to the study or the medications; five others received a daily dose of either glyburide (subjects 9–11) or glipizide (subjects 12 and 13) starting at 8:00 A.M. on the 1st postoperative day. Breast-feeding was begun at the same time. Each subject was discharged with a known amount of either nonmicronized glyburide (5 mg) or immediate-release glipizide tablets (5 mg). A nurse visited the subjects at home on the day of sampling. The morning sampling time was chosen to correspond to the longest period between doses and the longest time between infant feedings. Trough blood and milk samples were taken from the mother just before the next scheduled dose of medication. Using an electric breast pump (Medela Lactina Select Breast Pump; Medela, McHenry, IL), both breasts were emptied, the milk was pooled, and a 10-ml aliquot was taken for analysis. A blood sample (<1 ml) was also obtained from the infants by heel prick for glucose determination, and afterward the remaining milk was bottle-fed to the infant. After obtaining the mother's trough blood and milk samples and the infant's blood sample, the number of tablets remaining was counted and the subject was given the morning dose. The samples were placed on ice and immediately transported to the hospital laboratory. The nurse then returned to the subject's home at the time of the expected peak blood concentration (4 h after the glyburide dose and 3 h after the glipizide dose) and obtained maternal blood and milk samples. Again, these specimens were transported on ice to the hospital laboratory. In subject 9 (glyburide), the infant blood sample was not obtained because the infant had received formula to supplement breast-feeding. In subject 10 (glyburide), the blood sample was obtained from the infant and the glucose level was determined before it was learned that the

mother was supplementing nursing with formula. The MTID and the MTID as the percent of WAMD were calculated in the same manner as in the Toronto study; however, the limit of detection for the drug assays in serum and milk was 0.08 $\mu\text{g/ml}$.

Sample analysis

Single-dose study. Breast milk and serum samples were analyzed for glyburide concentration by high-performance liquid chromatography (HPLC) using a modification of the method by Susanto and Reinauer (6). Briefly, glyburide was extracted from 1-ml samples by liquid-liquid extraction with 5 ml of chloroform. Tolbutamide was added as an internal standard to all samples. Samples were vortexed and subsequently centrifuged and the organic phase was evaporated to dryness under a stream of nitrogen. The samples were reconstituted in 200 μl of freshly prepared NBD-Cl solution (1 mg/ml NBD-Cl in 1-octanol/amyI acetate [98:2 vol/vol]) and heated at 120°C for 80 min. Samples were then filtered using Millipore Ultrafree MC filters (Amicon; Millipore, Billerica, MA). A 10- μl aliquot was analyzed by HPLC using a Luna C-8 column (3- μm particles, 150 \times 4.6 mm; Phenomenex, Torrance, CA) equipped with a C-8 SecurityGuard cartridge (Phenomenex) and fluorescence detection (excitation = 470 nm and emission = 530 nm; Shimadzu, Kyoto, Japan).

The HPLC mobile phase consisted of 35% acetonitrile in water and was run at 0.5 ml/min. Analytes were quantified using the peak height ratio of glyburide to tolbutamide against a standard curve of breast milk or serum spiked with known concentrations of glyburide (0–500 ng/ml) and a fixed concentration of tolbutamide ($R^2 > 0.99$ for breast milk and serum). Analysis of the blank serum and blank breast milk showed no peaks that would interfere with analysis. The intraday coefficients of variation (CVs) were <5% for breast milk and serum both. The limit of detection was 0.005 $\mu\text{g/ml}$.

Daily-dose study. Serum and milk samples were analyzed by National Medical Services (Willow Grove, PA). Glyburide or glipizide and an internal standard were extracted into organic solvent, then evaporated and reconstituted, with mobile phase and subsequent analysis by HPLC with ultraviolet detection. The limit of detection for glyburide and glipizide in se-

Table 1—Single-dose glyburide study: maternal characteristics and estimated infant dose

| | Maternal dose 5 mg | | | | | | Maternal dose 10 mg | | | |
|----------------------|--------------------|-----------|-----------|-----------|-----------|-----------|---------------------|-----------|-----------|------|
| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 | Mean | Subject 7 | Subject 8 | Mean |
| Age (years) | 42 | 37 | 41 | 35 | 33 | 42 | — | 27 | 32 | 36 |
| Maternal weight (kg) | 68.9 | 122.5 | 90.0 | 83.8 | 86.5 | 93.2 | 90.8 | 59.6 | 103.7 | 81.7 |
| WAMD (mg/kg) | 0.07 | 0.04 | 0.06 | 0.06 | 0.06 | 0.05 | 0.06 | 0.17 | 0.10 | 0.14 |
| MTID as % WAMD | <1.1 | <2.0 | <1.4 | <1.3 | <1.4 | <1.5 | <1.5 | <0.5 | <0.8 | <0.7 |

The MTID, based on a detection limit of 0.005 $\mu\text{g}/\text{ml}$ and a milk intake of 150 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, is $<0.00075 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$.

rum and milk was 0.08 $\mu\text{g}/\text{ml}$. The interassay CV for glyburide in serum was 12.35 and 12.56% at concentrations of 0.5 and 2.0 $\mu\text{g}/\text{ml}$, respectively; in milk, the CV for glipizide was 9.85 and 8.85% at the same respective concentrations. The CV for both glyburide and glipizide in milk was $<5\%$ at concentrations of 0.8 and 2.0 $\mu\text{g}/\text{ml}$. Serum glucose concentrations were measured by an enzymatic procedure (Gluco-quant; Roche Diagnostics, Indianapolis, IN).

RESULTS

Single-dose study

The characteristics of the women in the single-dose glyburide study are shown in Table 1. The mean WAMDs were 0.06 and 0.14 mg/kg for the 5- and 10-mg doses, respectively. The maternal serum and milk concentration profiles are shown in Fig. 1. There were no blood samples available for patient 3, as she was seen in her home and the blood could not be processed in time. Of the 32 breast milk samples taken, 29 samples were available for analysis. Regardless of the dose, glyburide was not detected in any of the milk samples over the 8-h study interval. In contrast, the plasma levels were invariably detected. The mean MTID as the percent of WAMD for the 5- and 10-mg glyburide doses was <1.5 and $<0.7\%$, respectively.

Daily-dose study

The characteristics of the five subjects, the results of serum and milk assays and infant glucose levels, and the MTID as the percent of WAMD are shown in Table 2. Only subject 12 (glipizide) had a detectable serum level of the drug. Three wholly breast-fed infants (one glyburide, two glipizide) had normal blood glucose levels. Another infant (glyburide) had a normal blood glucose level, but the mother

had supplemented breast-feeding with formula. A glucose level was not measured in the other glyburide case because the mother disclosed before sampling that she also was supplementing with formula. Neither glyburide nor glipizide were detected in milk. The mean MTID as the percent of WAMD was <28 and $<27\%$ for the glyburide and glipizide subjects, respectively.

CONCLUSIONS— To date, the use of sulfonylureas during breast-feeding has been discouraged. Earlier studies with two first-generation sulfonylureas, tolbutamide and chlorpropamide, showed that there was significant transfer of these drugs into breast milk (7,8). In one study of chlorpropamide, the breast milk con-

centration was found to be 5 $\mu\text{g}/\text{ml}$ after a 500-mg oral dose (9). In another study of two women using tolbutamide 500 mg, breast milk concentrations were 3 and 18 $\mu\text{g}/\text{ml}$, with milk-to-plasma ratios of 0.09 and 0.40, respectively. The effect on the infants was not reported (8). Glyburide and glipizide, on the other hand, are second-generation sulfonylureas that are broadly used for the treatment of type 2 diabetes. The transfer of these agents into breast milk has not been studied, but the molecular weights of glyburide (~ 494) and glipizide (~ 446), as well as their elimination half-lives (glyburide ~ 10 h and glipizide 2–4 h) should support transfer. However, both agents are extensively bound by plasma proteins (98–99%) and have relatively short termination half-

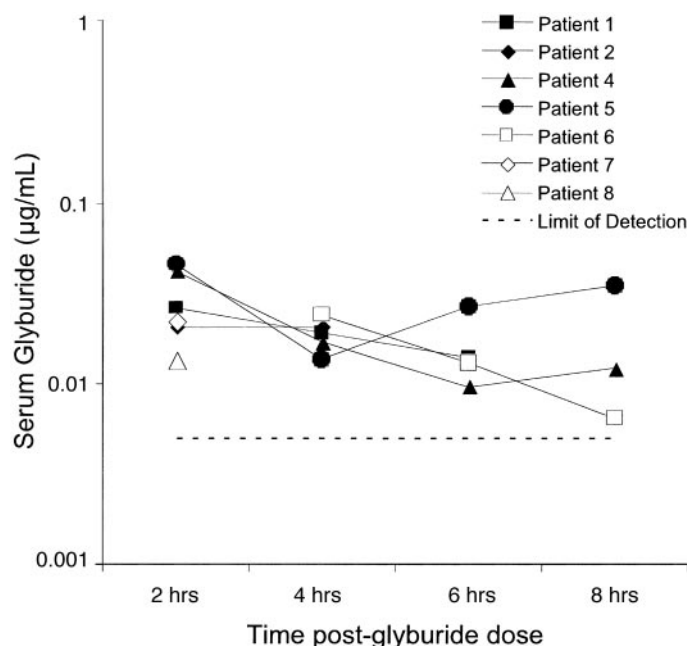


Figure 1—Serum concentration for glyburide after a single 5-mg (patients 1–6) and 10-mg (patients 7 and 8) oral dose. (No blood samples were available for patient 3, as she was seen in her home and the blood could not be processed in time.) All breast milk samples were below the detectable limit of 0.005 $\mu\text{g}/\text{ml}$.

Table 2—Daily-dose study: maternal characteristics, serum and milk levels, infant glucose, and estimated infant dose

| | Glyburide | | | Glipizide | |
|---|-----------|------------|------------|------------|------------|
| | Subject 9 | Subject 10 | Subject 11 | Subject 12 | Subject 13 |
| Weight (kg) | 66 | 182 | 101 | 103 | 118 |
| Age (years) | 26 | 34 | 32 | 30 | 37 |
| WAMD (mg · kg ⁻¹ · day ⁻¹) | 0.076 | 0.027 | 0.050 | 0.049 | 0.042 |
| Samples drawn POD | 5 | 8 | 7 | 7 | 16 |
| Serum peak/trough (μg/ml)* | ND/ND | ND/ND | ND/ND | ND/ND | 0.20/ND |
| Milk peak/trough (μg/ml)* | ND/ND | ND/ND | ND/ND | ND/ND | ND/ND |
| Infant glucose [mg/dl (POD)] | Not done† | 73 (8)† | 71 (7) | 65 (7) | 61 (16) |
| MTID as % WAMD‡ | <16 | <44 | <24 | <24 | <29 |

Data based on the detection limit and intake of 150 ml · kg⁻¹ · day⁻¹ of milk. *Detection limit was 0.08 μg/ml. †Mother supplemented feedings with formula. ‡MTID, based on the detection limit and a milk intake of 150 ml · kg⁻¹ · day⁻¹, is <0.012 mg · kg⁻¹ · day⁻¹. ND, none detected; POD, postoperative day.

lives (glyburide ~10 h and glipizide 2–4 h). Moreover, in vitro studies have shown that glipizide and glyburide do not cross the placenta in clinically significant amounts (10,11). Indeed, when glyburide was used to treat gestational diabetes, detectable levels were not found in cord blood (12,13). Taken in aggregate, these data suggest that neither drug will be excreted into breast milk in clinically significant amounts.

Although the two studies were conducted independently, they complemented each other. In the Toronto study, the sensitivity of the assay was much greater and confirmed low levels, whereas in the Long Beach study, the maternal drug levels were at steady state and data for nursing infants were included.

In these studies, neither glyburide nor glipizide were detected in breast milk. In the single-dose study, the lowest level of detection of glyburide in breast milk was 0.005 μg/ml. At this detection limit, the MTID of glyburide ingested is <0.00075 mg · kg⁻¹ · day⁻¹, representing a mean <1.5 and <0.7% of the mean WAMD of 5 and 10 mg/day, respectively. Because the infant therapeutic dose of most drugs (including glyburide and glipizide) is unknown, a clinically insignificant dose, if there are no data suggesting otherwise, is considered to be not >10% of the WAMD (milligrams per kilogram per day) (14). In the daily-dose study, the glyburide and glipizide detection limits were much higher (0.080 μg/ml), corresponding to an MTID of <0.012 mg · kg⁻¹ · day⁻¹. At this level, the mean MTID as the percent of WAMD (<28% for glyburide and <27% for glipizide) was reflective of the relative insensitivity of the assays. Because the amounts

of glyburide and glipizide excreted into milk should be similar based on their chemical characteristics, we believe that the glyburide and glipizide levels would have been undetectable at the 0.005-μg/ml level also if the daily-dose study had used the more sensitive assays. If so, the corresponding relation to the maternal dose would have been <1.0, <1.5, and <2.8% for the three glyburide-exposed infants and <1.5 and <1.8% for the glipizide-exposed infants, respectively. These estimated exposures for glyburide and glipizide are unlikely to exert a clinically significant pharmacological action and, in fact, no hypoglycemic effect was observed in the three nursing infants. Blood glucose was also normal in another glyburide-exposed infant for whom the mother was supplementing nursing with formula.

A limitation of the two studies was the small sample size. In the Toronto study, there were eight subjects, six receiving a 5-mg dose and two receiving a 10-mg dose. Variable amounts of fore-, mid-, and hindmilk were expressed. This may have influenced the concentration of glyburide in the milk; however, it was not likely that this was a large factor given the fact that glyburide was not found in any of the milk samples. Although only two of the eight subjects in the single-dose study had all four serum measurements done, the objective of this study was not to determine the pharmacokinetics of glyburide. In the Long Beach study, neither glyburide nor glipizide was detected in the breast milk of five subjects, and only one subject had a serum sample with detectable drug. The inability to detect serum concentrations is probably a result of the assay sensitivity. The finding with the

greatest clinical significance, however, was the normal blood glucose concentrations in the three infants who were wholly breast-fed.

To our knowledge, this is the first study to report the use of glyburide and glipizide during breast-feeding. Although additional data are required, the absence of detectable levels of either agent in breast milk and the presence of normal blood glucose levels in nursing infants leads us to conclude that immediate-release glyburide and glipizide, in the doses tested, are compatible with breast-feeding.

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