Use of hypoglycemic drugs during lactation

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ABSTRACT

QUESTION My patient was taking glipizide (an oral sulfonylurea) for type 2 diabetes. Now she is pregnant and taking insulin instead. She is very anxious to return to her previous treatment immediately after delivery because of the pain and hurdles associated with the administration of insulin. Can sulfonylureas cross into human milk and, if so, is it safe for her to breastfeed her infant?

ANSWER The exposure of infants to second-generation sulfonylureas (eg, glipizide, glyburide) through breast milk is expected to be minimal, based on the limited data available. Women with type 2 diabetes treated with sulfonylureas should not be discouraged from breastfeeding. The benefits of breastfeeding greatly outweigh the risks of these medications, if any. The baby should, however, be monitored for signs of hypoglycemia.

RÉSUMÉ

QUESTION Ma patiente prenait du glipizide (sulfonylurée par voie orale) pour un diabète de type 2. Elle est maintenant enceinte et prend plutôt de l’insuline. Elle a bien hâte de revenir à son ancien traitement et veut le faire immédiatement après l’accouchement à cause de la douleur et des embarras associés à l’administration d’insuline. Est-ce que les sulfonylurées peuvent passer dans le lait maternel et, dans l’affirmative, est-il sécuritaire pour elle d’allaiter son nourrisson?

RÉPONSE Selon les données limitées à notre disposition, on pourrait s’attendre à ce que l’exposition du nourrisson aux sulfonylurées de deuxième génération (p. ex., glipizide, glyburide) par l’intermédiaire du lait maternel soit minimale. Il ne faudrait pas décourager les femmes ayant un diabète de type 2 et traitées aux sulfonylurées d’allaiter leur enfant. Les avantages de l’allaitement dépassent largement les risques de ces médicaments, s’il en est. Il faudrait par ailleurs surveiller chez le bébé tout signe d’hypoglycémie.

Sulfonylureas are oral hypoglycemics commonly prescribed for type 2 diabetes mellitus, as they stimulate the release of insulin from the pancreas.1 These drugs are classified into first-generation (eg, chlorpropamide, tolbutamide) and second-generation agents (eg, glyburide, glipizide, glimepiride, and gliclazide). First-generation sulfonylureas are rarely used nowadays owing to a high incidence of adverse reactions. Second-generation drugs possess better safety profiles and are more potent than the older agents.2 Sulfonylurea act on the sulfonylurea receptor, an adenosine triphosphate–dependent potassium channel, stimulating the depolarization of pancreatic β cells and triggering insulin secretion via exocytosis.3 Sulfonylureas also inhibit hepatic clearance of insulin.4 Sulfonylureas are absorbed through the gastrointestinal tract quickly; they appear in blood within 15 minutes of ingestion but have a prolonged duration of action,4 especially the extended-release preparations. Sulfonylureas are mostly metabolized in the liver to metabolites excreted renally.5 Peak plasma concentrations of second-generation sulfonylureas occur within 2 to 4 hours of therapeutic doses.6 Duration of action is 12 to 24 hours.6,7 First-generation sulfonylureas have, to a limited extent, been shown to cross into breast milk. Tolbutamide is excreted into breast milk in small amounts (less than 0.5% of the maternal weight-adjusted dose). A 500-mg dose of tolbutamide twice daily produced milk levels of 3 and 18 µg/mL in 2 patients, with milk-to-plasma ratios of 0.09 and 0.40, respectively.8 In 1 patient, chlorpropamide was found in breast milk at concentrations of 5 µg/mL (approximately 10% of the maternal weight-adjusted dose) after a 500-mg maternal oral dose.9 No clinical effects to the exposed infants were reported. Transfer of second-generation sulfonylureas into breast milk has been studied, with similar results. A Motherisk study examining the transfer of glyburide and glipizide into breast milk failed to detect these drugs in breast milk.10 In a recent study,8 mothers who had recently delivered were given a single dose of glyburide, 5 mg (n=6) or 10 mg (n=2), and maternal blood and milk were tested at 8 hours after the dose. The
authors estimated that the maximum dose that a fully breastfed infant would receive with maternal 5- and 10-mg daily doses would be below 1.5% of the maternal weight-adjusted dose.10 Another group of mothers (N = 5) received daily doses of glyburide (nonmicronized 5 mg) or glipizide (immediate-release 5 mg). Neither glyburide nor glipizide could be detected in breast milk. Blood glucose levels were normal in all 3 infants who were exclusively breastfed (glyburide [n = 1], glipizide [n = 2]). Based on these data, maternal exposure to these drugs seems unlikely to exert any clinically significant pharmacologic action on breastfed infants.

Extensive binding of glyburide and glipizide to plasma proteins has been postulated as the reason for the observed lack of transfer of these drugs into breast milk.10

Sulfonylureas offer substantial therapeutic benefits to women with type 2 diabetes mellitus, and an expanding number of pregnant women are taking these medications for the treatment of gestational diabetes or type 2 diabetes during pregnancy.11 The benefits provided by these medications seem to outweigh the small theoretical risk posed by the minimal (if any) excretion of these drugs into breast milk. These medications are likely compatible with breastfeeding, provided that monitoring the baby for signs of hypoglycemia is feasible.12

Metformin with breastfeeding

Metformin is a widely used oral, biguanide hypoglycemic drug for the management of type 2 diabetes. Metformin stimulates glucose uptake in the liver and peripheral tissues and decreases hepatic glucose production. These actions are the result of an enhanced tissue response to insulin and therefore require the presence of insulin. Metformin is not expected to cause hypoglycemia.13

Three studies have evaluated the transfer of metformin into breast milk. In one study, 5 women taking a median dose of 1500 mg/d of metformin had average breast milk levels of 0.27 mg/L, amounting to an estimated 0.28% of the maternal weight-adjusted dose ingested by the infant. Very low or undetectable concentrations of metformin were observed in the plasma of the 4 babies studied.14 A second study looking at breast milk transfer of metformin enrolled 7 women who took 1000 mg/d of the drug. The milk concentrations observed were similar to those of the previous study, with estimated doses ingested by the infants below 1% of the maternal weight-adjusted dose.15 Another study involving 8 women (3 at steady state and 5 after single 500-mg doses of metformin) estimated that nursing infants would ingest about 0.11% to 0.25% of the maternal weight-adjusted dose.16

A recent prospective study followed 61 breastfed and 50 formula-fed infants born to 92 mothers with polycystic ovary syndrome taking 1.5 to 2.55 g of metformin daily throughout pregnancy and lactation.17 The authors concluded that metformin use during lactation had no adverse effects on breastfed infants’ growth, motor-social development, or intercurrent illnesses, compared with formula-fed infants.

Metformin is considered a first-line agent for the treatment of type 2 diabetes,13 and has also been proposed as a useful drug for the management of gestational diabetes.18 The very limited amounts of metformin observed in breast milk are highly unlikely to lead to substantial exposure in the breastfed baby. Metformin can be considered a safe medication for the treatment of type 2 diabetes in a breastfeeding mother.

Conclusion

The available data suggest that the levels of glyburide and glipizide in milk are negligible and would not be expected to cause adverse effects in breastfed infants; however, as data are based on a single study with a limited sample size, monitoring of the breastfed infant for signs of hypoglycemia is advisable during maternal therapy with any of these agents.

Treatment with metformin during lactation is unlikely to lead to toxicity in the breastfed infant. Given the safety profile of metformin, as compared with sulfonylureas, it is advisable to consider metformin as first-line treatment during lactation if this drug is appropriate for the particular patient. Nevertheless, second-generation sulfonylureas are also likely to be safe during lactation.

Other oral medications currently used for the treatment of type 2 diabetes, such as the thiazolidinediones and acarbose, have not been studied in the lactation period.

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Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future Motherisk Updates.

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Motherisk Update

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Competing interests
None declared

References