Pharmacologic treatment of hyperthyroidism during lactation

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ABSTRACT

QUESTION I have a patient who has hyperthyroidism due to Graves disease. She was taking methimazole but discontinued when she found out she was pregnant. She is currently close to delivery and might require antithyroid therapy in the postpartum period. Can methimazole cross into human milk, and is breastfeeding safe for her infant?

ANSWER The exposure of infants to methimazole or propylthiouracil through breast milk is minimal and not clinically significant. Women with hyperthyroidism using methimazole or propylthiouracil should not be discouraged from breastfeeding, as the benefits of breastfeeding largely outweigh the theoretical minimal risks.

RÉSUMÉ

QUESTION Une de mes patientes fait de l'hyperthyroïdie à cause de la maladie de Graves. Elle prenait du méthimazole, mais a cessé quand elle a appris qu'elle était enceinte. Elle accouchera bientôt et pourrait avoir besoin d'une thérapie antithyroïdienne après la naissance. Le méthimazole est-il transmis dans le lait maternel, et l'allaitement est-il sans danger pour le nourrisson?

RÉPONSE L'exposition des nourrissons au méthimazole ou au propylthiouracil dans le lait maternel est minimale et peu significative sur le plan clinique. Il ne faut pas décourager les femmes atteintes d'hyperthyroïdie qui prennent du méthimazole ou du propylthiouracil d'allaiter puisque les bienfaits de l'allaitement dépassent largement les risques théoriques minimaux.

Methimazole and propylthiouracil are selective inhibitors of thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin, which reduce the production of thyroid hormone. They are effective in the treatment of different etiologies of hyperthyroidism.[1] Thioamides also inhibit the coupling of these iodotyrosyl residues to form iodothyronines.[2] In addition to blocking hormone synthesis, propylthiouracil, unlike methimazole, inhibits the peripheral deiodination of thyroxine (T_4) to triiodothyronine.[3] These drugs—including carbimazole, a prodrug of methimazole—belong to the thioamide group.[4] All drugs in this class have similar efficacy and safety but differ in potency and duration of action. Methimazole has a longer elimination half-life and can be given once daily.[5] At low doses, adverse effects are less commonly described with methimazole and carbimazole when compared with propylthiouracil,[4] and the infrequent drug-related hepatitis and vasculitis appear to occur relatively more commonly with propylthiouracil.[6] Certain β-adrenergic antagonists (not including atenolol or acebutolol), such as propranolol, can be safely used as adjunctive therapy during breastfeeding.[7]

Absorption of thioamides through the gastrointestinal tract is rapid; these drugs appear in the blood within 30 minutes of administration of oral doses and have a quick onset of action.[8] Thioamides are metabolized in the liver to inactive metabolites that are excreted renally. The half-life of propylthiouracil in plasma is about 75 minutes, whereas for methimazole it is 4 to 6 hours.[8-10] Mean peak plasma concentration of propylthiouracil after a 200-mg dose is 6.5 µg/mL[9,11]; a 40-mg oral dose of methimazole produced a peak plasma concentration of 0.54 µg/mL.[10]

Breastfeeding

For many years breastfeeding was strongly discouraged if treatment with antithyroid drugs was required.[12] Both propylthiouracil and methimazole can be detected in milk[13-15]; however, studies have shown that propylthiouracil crosses into milk only in minute amounts, leading to a milk-plasma ratio of approximately 0.1.[15] A woman taking 200 mg/d of propylthiouracil and feeding a baby daily with 150 mL/kg of breast milk would transfer less than 3% of her weight-adjusted dose of propylthiouracil to her infant.[16] No adverse effects on neonatal thyroid status in breastfed infants were

reported even at high maternal doses of 750 mg/d of propylthiouracil.[14]

Methimazole, on the other hand, has a milk-plasma ratio close to 1[15]; a woman taking 40 mg/d of methimazole and breastfeeding a volume of 150 mL/kg daily to her baby would transfer a maximum of 12% of her weight-adjusted dose through breast milk. Azizi[17] showed in one study of 35 infants of lactating mothers with thyrotoxicosis who were treated with methimazole daily that all babies maintained normal thyroid functions in spite of breastfeeding. In another study,[18] no deleterious effects were observed in thyroid function or physical and intellectual development up to 48 to 74 months of age in breastfed infants whose mothers were treated with up to 20-mg/d doses of methimazole. Lamberg et al[19] reported outcomes for 11 infants whose mothers were treated with carbimazole (which converts to methimazole in circulation) at dosages ranging from 5 to 15 mg daily during pregnancy and after delivery. All infants in this study had normal serum thyrotropin and T_4 levels. Based on these observations, it has been proposed that methimazole (preferably in low dosages) could be used during breastfeeding if the infant's thyroid status is monitored.[20]

Conclusion

Thioamides offer substantial therapeutic benefits to women with hyperthyroidism. On the basis of all the current literature, we conclude that either propylthiouracil or methimazole administered to lactating women is likely to be safe for their infants. Careful monitoring of both mother and infant is still advisable, including serum T_4 and thyrotropin determinations at least 3 to 4 weeks after initiation of breastfeeding.

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Competing interests

None declared

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Giglio** is a staff physician at the Hospital de Niños "Ricardo Gutiérrez" in Buenos Aires, Argentina. **Drs Glatstein, Garcia-Bournissen,** and **Finkelstein** are members and **Dr Koren** is Director of the Motherisk Program. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation. He holds the Ivey Chair in Molecular Toxicology in the Department of Medicine at the University of Western Ontario in London.

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