Comment: Breast-feeding During Maternal Use of Azathioprine

TO THE EDITOR: Information on the safety of immune-suppressing drugs in breast-feeding is generally lacking. Many authors consider this class of drugs to be contraindicated during breast-feeding because of the drugs' low therapeutic index and theoretical concerns about long-term safety.[1] Therefore, we commend Moretti et al.[2] for their case series describing the lack of adverse outcomes in 4 infants whose mothers took azathioprine while breast-feeding. However, we wish to comment on their use of 6-mercaptopurine (6-MP) concentrations in milk as their means of assessing infant exposure in 2 of the mother–infant pairs.

The authors stated that mercaptopurine, the initial product of azathioprine, was the major active metabolite. This is not the case. It is the thioguanine nucleotides (TGNs) enzymatically produced from mercaptopurine that are thought to be responsible for most of the immunosuppressive effects of these drugs.[3] Mercaptopurine itself is regarded as inactive.[4] Despite this inaccuracy, failure to detect mercaptopurine (limit of detection 5 μg/L) in the milk of 2 mothers is reassuring and confirms a low infant "dose" of mercaptopurine in milk (<0.1% of the maternal dose, corrected for weight).[2]

We too have studied the likely safety of azathioprine in breast-feeding, but elected to focus on infant exposure to the active TGNs. We reasoned that the TGNs would be unlikely to be detected in milk given that they reside intracellularly. Therefore, we sampled blood from 6 mother–infant pairs (n = 4[5] and n = 2 [unpublished]) for determination of TGN concentrations during maternal use of azathioprine 1.2–2.1 mg/kg/day. Thiopurine methyltransferase (TPMT) genotype (a major determinant of TGN concentrations) and concentrations of the potentially hepatotoxic metabolites methylmercaptopurine nucleotides (MMPN) were also determined. All mothers and their infants (~3 mo of age) had the wild-type TPMT genotype, suggesting that "normal" exposure to the TGNs should be expected. Both TGNs and MMPNs were below the limit of quantification (30 pmol/8 × 10^8 red blood cells) in all 6 infants, whereas maternal concentrations were consistent with therapeutic exposure (234–449 and 284–1342 pmol/8 × 10^8 red blood cells, respectively). No adverse effects were detected in any of the 6 infants.[5]

The consistent findings of both studies, in terms of the undetectable concentrations of the inactive mercaptopurine in milk[2] and the active TGN in infant blood,[5] are reassuring. The results suggest that azathioprine may be safely used in breast-feeding in mother–infant pairs with the wild-type TPMT genotype. The availability of sensitive assays for TGN concentrations in some centers offers a valuable means of objectively assessing infant exposure during clinical use and could be used in conjunction with other clinical assessments. Clearly, risk–benefit assessment remains essential in all cases. Further study is warranted, especially among mother–infant pairs with intermediate or deficient TPMT genotypes who may achieve greater exposure to mercaptopurine and the active TGN metabolites for a given azathioprine dose.

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.–ED.

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AUTHORS' REPLY: We thank Gardiner et al. for their interest in our article. Their recent work helps clinicians to see a more complete picture of this exposure and enables them to be more reassuring. We agree with the authors that the toxic active metabolites of azathioprine are the TGNs produced from mercaptopurine. However, as they correctly state, these active metabolites are incorporated intracellularly and are not likely to be found in milk. These metabolites are also unlikely to be absorbed by the infant. Therefore, although measurements of mercaptopurine do not provide us with an absolute infant exposure to the toxic metabolite, it is the mercaptopurine present and ingested from breast milk that would be converted by the infant to the more toxic TGN. Considering that we[1] and others[2,3] have found very low or undetectable concentrations of mercaptopurine in breast milk, it is not surprising that Gardiner et al. could not detect 6-TGN in the breast-fed infants.

Ultimately, it can be reassuring for clinicians and patients that these infants do not appear to have exposures that are clinically toxic. In particular, since the infants of mothers taking immunosuppressants are frequently born prematurely, these are the very infants who may benefit the most from receiving breast milk.

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Comment: Oral Varenicline for Smoking Cessation

TO THE EDITOR: We would like to comment on the recent review by Drs. Zierler-Brown and Kyle[1] of varenicline, an $\alpha_4\beta_2$ nicotinic receptor partial agonist.

First, in their brief discussion of nicotine replacement therapy, they correctly state that, "Nicotine replacement therapy delivers nicotine to the body at various rates, depending on the formulation," but incorrectly state that nicotine replacement "...lacks the addictive constituents found in tobacco, thereby minimizing the potential for addiction." While it is true that the slower rate of nicotine delivery from nicotine replacement products reduces risk of dependence, it is also well established that nicotine, rather than other constituents in tobacco, is the drug primarily responsible for dependence.[2]

In their discussion of the interactions between varenicline and nicotine replacement therapy, the authors report that varenicline pharmacokinetics was unaffected when varenicline was concurrently administered with nicotine replacement therapy. In fact, however, the cited study only reported the effect on nicotine pharmacokinetics with coadministration of nicotine replacement therapy with varenicline.[3]

In Table 3, the authors attempt to summarize the 3 studies reported in *JAMA*. Two of the trials, listed together, were identical in design.[4,5] Although the results were similar, only one of the trials was discussed.[4] In addition, the dosing regimen in the 2 trials was 0.5 mg once daily for days 1 to 3, 0.5 mg twice daily for days 4 to 7, and 1.0 mg twice daily from day 8 through week 12. In these 2 studies, treatment was for only 12 weeks[4,5]; therefore, the statement that "discontinuations due to nausea occurred in 3% of subjects beyond 12 weeks of therapy" is not correct. The discontinuations refer to all subjects. In addition, an article having to do with nicotine replacement therapy is cited in support of varenicline data.[6]

Finally, the authors' summary conclusion that "varenicline shows efficacy comparable to that of bupropion SR and superior to that of placebo" is not really consistent with the findings. As the authors note, varenicline has been shown to be significantly more efficacious than bupropion at 12 and 24 weeks[4,5] by 2 studies and at 52 weeks[5] by one study.

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Dr. Gonzales has received research contracts from Pfizer, Sanofi-Aventis, GlaxoSmithKline, Addex Pharmaceuticals, and Nabi Biopharmaceuticals and consulting fees and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline and owns 5 shares of Pfizer stock. Dr. Rennard has participated as a speaker in scientific meetings and courses under the sponsorship of AstraZeneca and GlaxoSmithKline; serves on advisory boards for Altana, AstraZeneca, Dey GlaxoSmithKline, and Inspire; has conducted clinical trials for AstraZeneca, Centocor, GlaxoSmithKline,