CORRESPONDENCE

Re: Active Tamoxifen Metabolite Plasma Concentrations After Coadministration of Tamoxifen and the Selective Serotonin Reuptake Inhibitor Paroxetine

The article by Stearns et al. *(1)* provides evidence that the tamoxifen metabolite endoxifen (4-hydroxy-*N*-desmethyltamoxifen) is equipotent with 4-hydroxytamoxifen in inhibiting estradiol-stimulated MCF7 cell proliferation. Further, they show that paroxetine can potentially interfere with metabolism of tamoxifen to endoxifen through an inhibition of CYP2D6. Stearns et al. *(1)* speculate that, as a result, coadministration of tamoxifen and paroxetine might decrease the therapeutic value of tamoxifen treatment. Because paroxetine has a valuable role in controlling hot flashes, a common side effect of tamoxifen treatment, the article by Stearns et al. *(1)* provides important information for the many women taking tamoxifen and taking or considering paroxetine or other selective serotonin reuptake inhibitors (SSRIs).

Tamoxifen is a selective estrogen receptor modulator used in the treatment of estrogen receptor–positive breast cancer in both metastatic and adjuvant settings. The breast cancer prevention trial showed that women who received tamoxifen had a 45% reduction in breast cancer occurrence *(2)*. Although tamoxifen is an active agent against breast cancer, its exact mechanism(s) of action is still unknown. Tamoxifen appears to have both cytostatic and cytotoxic activity. The "classic" mechanism of estrogen and anti-estrogen action requires that the ligand–receptor complex binds to defined promoter elements and modulates transcription. This mechanism appears to have cytostatic effects *(3)*. Tamoxifen has also been shown to be cytotoxic, initiating apoptosis in estrogen receptor–positive breast cancer cells and acutely damaged, estrogen receptor–poor normal human breast epithelial cells *in vitro (4,5)*. We have recently shown that apoptosis induced by tamoxifen is independent of the classic pathway of tamoxifen action, involved plasma membrane–mediated regulation of AKT, mitochondrial depolarization, and caspase activation *(5,6)*.

In the study by Stearns et al. *(1)*, the serum concentrations of tamoxifen, *N*-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen were approximately 155, 180, 1.1, and 12 ng/mL, respectively. The K_d of tamoxifen for the estrogen receptor is 4.5 n*M*, approximately the same as that for *N*-desmethyltamoxifen, whereas the K_d of 4-hydroxytamoxifen is 0.15 n*M (6)*. With these values, estrogen binding to the estrogen receptor would be effectively blocked by tamoxifen or any of the noted metabolites. Therefore, a decrease in the concentration of endoxifen would not substantially affect estrogen receptor function. Given this information and the unknown role of endoxifen in treatment, we agree with Stearns et al. *(1)* that the use of paroxetine or other SSRIs should not be discontinued in patients receiving tamoxifen.

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Stearns et al. *(1)* provide convincing evidence on the influence of paroxetine, a selective serotonin reuptake inhibitor (SSRI), in the metabolic pathway of tamoxifen when administered to patients with breast cancer. In particular, they found that paroxetine decreased the plasma concentration of a metabolite they termed endoxifen (4-hydroxy-*N*-desmethyl-tamoxifen) by inhibiting cytochrome CYP2D6 activity. The authors suggest that endoxifen could be at least as active as 4-hydroxy-tamoxifen, another metabolite that is believed to play a major role in mediating the effects of tamoxifen. Indeed, they found that both metabolites had comparable *in vitro* antiestrogenic activity but that endoxifen concentrations were 14-fold higher in the plasma of patients receiving tamoxifen. Paroxetine led to a more pronounced reduction in endoxifen levels in women with a wild-type CYP2D6 genotype than in women with a variant genotype, who had lower endoxifen concentrations irrespective of paroxetine coadministration. Therefore, the authors concluded that pharmacologic (i.e., paroxetine) and genetic (i.e., CYP2D6 variants) factors may influence therapeutic outcomes from tamoxifen treatment.

We fully agree with their cautious final statement that until further data

become available, the results of this small study should not alter treatment recommendations. The minimal active dose of tamoxifen is unknown, and although an overview of clinical trials revealed that the conventional dose of 20 mg/day has comparable activity to higher doses of the drug *(2)*, clinical data on the efficacy of lower doses are lacking. It has been shown that, in healthy volunteers, reducing the conventional tamoxifen dose by up to 75% does not affect the concentration of insulin-like growth factor 1, a putative surrogate marker of breast cancer risk *(3)*. Furthermore, tumor expression of Ki-67, a marker of cell proliferation, was reduced in patients with breast cancer who received tamoxifen doses of 1 and 5 mg/day *(4)*. The magnitude of the reduction was not statistically significantly different from that achieved with the conventional dose of 20 mg/day *(4)*. The control of menopause-associated symptoms in breast cancer survivors is important and is an issue that has been greatly understudied. Hormonal remedies have not traditionally been used for breast cancer survivors with menopause-associated symptoms because of the possible risk of inducing cancer recurrence. It is reassuring that clinical data to support such a possible risk are rare *(5)*. Several nonhormonal remedies, including SSRIs, have proven effective in clinical controlled trials, but according to a survey we conducted in Italy, their use is still hampered by disinformation and unjustified concerns expressed by the patients and their doctors *(6)*. Good experimental data, such as those provided by Stearns et al. *(1)*, are essential to understanding the pitfalls of endocrine therapy for breast cancer, but they should not be used to prevent patients from taking drugs that may substantially improve their quality of life.

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In a recent study by Stearns et al. *(1)*, the authors identified the tamoxifen metabolite 4-hydroxy-*N*-desmethyl-tamoxifen. The authors stated that this active metabolite had not been previously recognized, and they named it endoxifen. However, 4-hydroxy-*N*-desmethyl-tamoxifen was observed in human breast tumor tissue by Mauvais-Jarvis et al. *(2)* and termed desMeOHTAM in 1986. This compound was already known to have a high affinity toward the estrogen receptor in 1982 *(3)*.

We reported in 1989 that 4-hydroxy-*N*-desmethyl-tamoxifen could be found in human biologic fluids and tissues and demonstrated that aminoglutethimide, a first-generation aromatase inhibitor, decreased its formation *(4–6)*. Because 4-hydroxy-tamoxifen was designated metabolite B and *N*-desmethyl-tamoxifen was designated metabolite X *(7)*, we called 4-hydroxy-*N*-desmethyl-tamoxifen metabolite BX.

We believe that the introduction of an additional name (i.e., endoxifen) for 4-hydroxy-*N*-desmethyl-tamoxifen will lead to confusion and propose, therefore, that the abbreviation 4OHNDtam should be used in the future.

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RESPONSE

We thank all three correspondents for their useful insights into our work. The data we presented demonstrate that the tamoxifen metabolite 4-hydroxy-*N*-desmethyl-tamoxifen (endoxifen) is equipotent to 4-hydroxy-tamoxifen in inhib-

iting estradiol-stimulated growth of MCF-7 cells *(1)* and that endoxifen concentrations were reduced in women who carried a genetic variant of CYP2D6 or in women with a wild-type CYP2D6 after coprescription with the CYP2D6 inhibitor paroxetine. The role of the parent drug tamoxifen, each of its metabolites, or a profile of the metabolites in inhibiting breast cancer progression remains unclear and is a critical area for future research. We thank Ratliff et al. for their elegant review of tamoxifen effects and agree that tamoxifen's mechanism of action is complex and that the high concentration of the parent drug and its primary metabolites may mean that they contribute to tamoxifen effects. Tamoxifen and its metabolites are concentrated in breast tissue, but determining which concentrations are active at the effect site remains elusive. The drug behaves as a weak antiestrogen in clinical trials, suggesting that its effects may be modulated by changes in its concentration or in concentrations of estradiol and other active species at the effect site. As we stated in the discussion of our paper, we agree that the implications of a reduction in endoxifen concentrations are unknown and should not affect current prescribing practices.

We agree with Dr. Ponzone and colleagues that the minimal active dose of tamoxifen is not known. These authors have reported that tamoxifen administered in doses lower than 20 mg/day demonstrated a similar effect on surrogate markers such as circulating insulin growth factor and tissue proliferation index Ki-67 *(2,3)*. However, studies to correlate serum and tissue surrogate markers with clinical outcomes such as disease-free or overall survival in women with breast cancer or a reduction in the incidence of breast cancer in those at high risk are not available. It is important to evaluate the metabolic profiles of tamoxifen with lower than standard does, and this is an area of continuing research.

In our study, we separated, purified, and identified the tamoxifen metabolite 4-hydroxy-*N*-desmethyl-tamoxifen,
which we designated endoxifen, as a metabolite whose concentration was decreased when patients were coprescribed paroxetine, a CYP2D6 inhibitor. The presence of the metabolite was apparent in the 1980s and, as Lien and colleagues report, was previously designated BX. We were asked by the reviewers of JNCI to name this metabolite to reduce the difficulty of reading the article. We thank these investigators for pointing out their earlier work, which is consistent with our own and enhances the potential clinical relevance of our work. In a second paper that specifically focused on comprehensive pharmacological characterization of 4-hydroxy-*N*-desmethyl-tamoxifen, we have referred in detail to the work conducted in the 1980s *(4)*. Lien et al. quantified 4-hydroxy-*N*-desmethyl tamoxifen in rat and human tissues in 1991 *(5)*. Although their data differ from ours in that BX was detected in only five of 11 human serum samples tested, it had a mean concentration in those samples that was 5.3-fold greater than that of B (4-hydroxy-tamoxifen), consistent with our data. In the interaction study between tamoxifen and aminoglutethimide reported by these authors, they showed a two- to threefold reduction in the area under the curve (AUC) concentrations of tamoxifen, *N*-desmethyl-tamoxifen, and 4-hydroxy-tamoxifen, and a 15-fold reduction in the AUC of 4-hydroxy-*N*-desmethyl-tamoxifen *(6)*. They speculated that these changes might be responsible for the documented lack of benefit seen in clinical trials when tamoxifen was coprescribed with aminoglutethimide, suggesting that the marked reduction in active metabolite concentrations seen in our study may also be important.

Given the proven benefits of tamoxifen in reducing mortality in patients with established invasive breast cancer and in reducing recurrences and new breast cancers in women with *in situ* lesions or other high-risk features, it will be difficult to address the effects of pharmacogenomics on these outcomes in a placebo-controlled trial. However, we are currently evaluating drug–gene interactions in a prospective cohort registry study of women who are taking tamoxifen for routine indications, and we hope that this study will provide further insights into the effects of pharmacogenetics on secondary endpoints, such as measures of estrogenic and/or anti-estrogenic activity.

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