Estrogen and Adenosine Triphosphate–Sensitive Potassium Channels

To the Editor:

We read with interest the publication by Lee et al.1 describing the potential mechanisms and effects of intracoronary conjugated estrogens on coronary vasomotion and myocardial ischemia in patients undergoing percutaneous coronary angioplasty. We were surprised at the very high bolus dose of intracoronary Premarin (Wyeth-Ayerst) given—5 mg into the left coronary system (postmenopausal replacement doses, given orally, range from 0.625 to 1.25 mg daily). The initial exposure dose to the coronary circulation would have been enormous; however, the local concentrations of estrogens are not discussed. It is important and relevant to the interpretation of this study to distinguish between acute, pharmacological effects and long-term replacement effects. How can the authors state that physiological levels of estrogen were achieved? They report that “end-study” coronary sinus 17β-estradiol levels were raised in their subjects (mostly male) receiving Premarin, but the levels exceed that reported in women taking oral replacement.2 The authors state that the levels achieved were similar to those of premenopausal women and were, therefore, physiological.

The other point to note is that Premarin is a mixture of several conjugated equine estrogens and is not known to contain 17β-estradiol. It is metabolized mainly to estrone, which then is converted to other estrogens, including 17β-estradiol.2 The authors, therefore, were wrong in measuring estradiol without also measuring estrone. Blood sampling for measurement of estradiol levels was performed “at the end of the study,” but no time period after administration of Premarin is given. This is vital information for determining whether conversion of Premarin would have occurred. We, therefore, feel that the clinical relevance of this study must be interpreted with caution.

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Response

We appreciate the critical reflection on our work.1 We really know that estrogen levels affect the biological response. To avoid use of supraphysiological doses of estrogen in this study, a pilot study was performed using different doses of Premarin (Wyeth-Ayerst) assessed by measuring the estradiol levels.2 Intracoronary injection of 5 mg of Premarin resulted in an increase of plasma estradiol concentration similar to those in women during ovulatory phase.3 Our results were compatible with those of Al-Khalili et al.,4 showing that intravenous administration of 5 mg of Premarin increases estradiol levels to a magnitude comparable to the midfollicular and preovulatory peak in the normal cycle. Premarin is extracted from the urine of pregnant mares and contains classical estrogen (45% estrone sulfate, 25% equilin sulfate, 15% 17α-dihydroequilenin, and lesser amounts of the sulfate esters of equilenin, 17β-dihydroequilenin, 17β-dihydroequilin, 17α-estradiol, and estradiol5) and ring B unsaturated estrogens. The conversion between estradiol and estrone is catalyzed by 17β-hydroxysteroid dehydrogenase in peripheral tissues. Previous studies have shown in humans that the estrone levels peaked 5 minutes after intravenous administration of Premarin, and a plateau level followed.4 A significant increase in 17β-estradiol levels was observed 5 minutes after administration,4 which further increased at the end of the study, ~60 minutes after administration. Because of the time period in pharmacokinetics of Premarin, we had a 10-minute drug-free period before angioplasty to allow a stable level of estrone, in spite of their minor role in modulating ionic channels compared with 17β-estradiol.5 Since all of the estrogens present in Premarin have estrogenic activities, the effects of Premarin are a result of the sum of these individual activities. To reflect the fact, we used conjugated estrogens in the title instead of 17β-estradiol.

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