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Meeting abstract

Preliminary exploration into the physiology of the resting breast

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Background

Epidemiological and animal data are clear that early first pregnancy decreases subsequent breast cancer risk. The mechanism for this decrease however is less clear and several hypotheses abound. One possibility that has not received any attention is the physiology of fluid secretion in the breast. The ductal systems have secretions which can be accessed either through nipple aspiration or ductal lavage. It is not clear whether the mechanisms identified for absorption, secretion, concentration and local synthesis that have been described in the lactating breast are consistently available to the non lactating breast or whether there is a difference in nulliparous and parous women. It is not clear whether the known changes to the ductal-alveolar system with the first pregnancy remain permanent or have long lasting ramifications. The hypothesis tested was that the first pregnancy permanently changes the physiology of the ductal epithelial membrane transport. Two known drug transport mechanisms in lactating women were tested using caffeine and cimetidine.

Methods

A total of 14 women were recruited for this IRB-approved prospective study to undergo blood collection, nipple aspiration and ductal lavage five times over 12 hours. Of these women, 5 were postmenopausal and 9 were premenopausal; 8 were parous and 6 nulliparous. Subjects were asked to abstain from caffeine and cimetidine for 24 hours prior to participation. After a baseline was recorded; subjects were then given 200 mg of caffeine (NoDoz) and 200 mg of cimetidine (Tagamet) and the procedure was repeated at set time points 4 more times over 12 hours. Samples were sent to a central laboratory for analysis where caffeine and cimetidine were quantified in serum, nipple aspirate fluid (NAF) and lavage.

Results

There were significant and intriguing results regarding the differences between the "resting" or non lactating breast and the lactating breast. In lactating women caffeine passively diffuses into milk rapidly and reflects serum levels. In resting breasts caffeine levels generally peak at 6 hours or later after ingestion. Cimetidine, on the other hand, is known to be concentrated in milk in the lactating woman but was not detected in ductal fluid from the resting breast. Since cimetidine is known to be actively transported in the lactating woman, this pattern is consistent with a transporter protein which is transcribed only during lactation. The concentrations and time course of drugs in NAF and DL also seem to differ suggesting some physiological difference other than dilution. There was a significant difference between parous and nulliparous women in terms of caffeine concentrations and uptake. Finally preliminary analyses of injected mannitol into breast ducts are still undergoing investigation to better understand the bidirectional transfer of drugs.

Conclusion

Our study has reinforced our opinion that the physiology of the "resting" breast is understudied and the transport mechanisms of drugs, vitamins or other nutrients in the non-lactating breast may be very different than the known mechanisms in a lactating woman. While different transport mechanisms, including passive diffusion, carrier-

mediated and transcytosis have been identified in the lactating breast no one that we are aware of has studied these routes in the female "resting" breast. Our pilot data with three drugs has lead to more questions than answers that we plan on probing further. This information is not only critical for potential understanding of systemic drug delivery to the breast for prevention or early intervention but also for the growing field of intraductal therapy.

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