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Abstract

Background: CDB4124, a progesterone receptor modulator, suppressed the development of precancerous lesions and carcinogen-induced ER+ mammary tumors in rats, and may have implications for prevention and treatment of human breast cancer; however, liver toxicity in human is the major problem of systemic delivery, and transdermal local delivery to the breast may be an excellent solution. We tested transdermal CDB4124 for in vitro human skin permeation and in vivo tissue distribution in rats compared to s.c delivery.

Methods: We tested CDB4124 (Repros Therapeutics, Inc.) alone and with ethanol and 0.5 v/v % oleic acid (OA) using split-thickness skin from mastectomy specimens, mounted in Franz diffusion cells (PermeGear, PA, USA). 0.5mg of CDB4124 in 60% alcoholic solution +/- OA and applied to the donor chamber. Aliquots of the receiver solution were collected at predetermined time points for 24 hr. Next, we tested the in vivo permeation of gel formulation of CDB4124 + 0.5% OA in nude rats comparing daily transdermal delivery (0.3mg/day) with a s.c pellet (30mg) for 6 weeks. Plasma and mammary fat pads (MFPs) were collected. CDB4124 and its major metabolite CDB4453 were quantified by LC-MS/MS.

Results: The permeation through human breast skin was 3.1±0.9% for CDB4124 alone and enhanced 4-fold to 11.6±1.5% with the addition of 0.5% OA at 24 hr. The rate of CDB4124 permeation was 5-fold faster than the drug alone within 12 hr. Plasma levels of CDB4124 were 14±5 and 11±5 ng/mL for the pellet and gel groups, respectively (p=0.16); plasma level of CDB4453 was higher in the pellet group than in the gel group, 4.6±2 vs. 1.5±0.6 ng/mL (p=0.000). CDB4124 levels in the upper MFP (the site of gel application) were 34-fold higher in the gel group than in the pellet group (1485ng/g for gel group; 44ng/g for pellet group, p=0.000); CDB4124 levels in the lower MFP were 194 ng/g for gel group; 66 ng/g for pellet group. CDB4124 and CDB4453 levels in upper MFP were significantly higher than in lower MFP (about 8-fold for CDB4124 and 7-fold for CDB4453; p=0.000, p=0.000, respectively). In contrast, the pellet group shows a similar concentration of CDB4124 and CDB4453 in the upper and lower MFPs.

Conclusions: This is an encouraging result because skin permeation of CDB4124 is similar to the level of estradiol, an efficacious transdermal agent, and indicating more extensive metabolism of CDB4124 when administered systemically. The high CDB4124 tissue level in the gel group indicate...
the possibility that drug smeared on the skin area other than the upper MFP, but the higher level of the metabolite CDB4453 supports the conclusion that a significant portion of the drug measured in the fat pad was in fact delivered to the tissue. Local transdermal delivery of CDB4124 seems plausible method for breast cancer prevention.


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