LEVORMELOXIFENE INHIBITS VAGINAL ELASTIN PRODUCTION

Hypothesis / aims of study: Clinical trials revealed that levormeloxifene treatment results in a significant increase in the rate of pelvic organ prolapse and urinary incontinence [1]. Our aim was to measure the effects of levormeloxifene on vaginal smooth muscle cell (SMC) proliferation, elastin and transforming growth factor (TGF)-β1 production. We hypothesized that levormeloxifene inhibits elastin and TGF-β1 production and this mechanism may contribute to the development of prolapse and incontinence.

Study design, materials and methods: Primary SMC cultures were performed from vaginal wall biopsies, grown to confluence and characterized by immunocytochemistry with primary antibodies against caldesmon, desmin and smooth muscle actin to verify the smooth muscle phenotype. SMC were incubated with levormeloxifene (0.1 µM, 1 µM), in 96-well plates and cell proliferation was assessed by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazoliumbromide (MTT) assay at 24 hrs. Supernatants were collected and elastin production was measured by the Fastin Elastin Assay kit and TGF-β1 levels were assessed by ELISA.

Results: SMC proliferation was significantly increased by levormeloxifene [relative cell number, mean±SE, levormeloxifene 0.1 µM 130±13% of control (P=NS), 1 µM 151±19% of control (P<0.05)]. Elastin production was significantly decreased by levormeloxifene [mean±SE, levormeloxifene 0.1 µM 75±4% of control (P=NS), 1 µM 64±2% of control (P<0.05) Figure 1]. In addition, TGF-β1 production was significantly decreased [mean±SE, levormeloxifene 0.1 µM 79±11% of control (P=NS), 1 µM 72±14% of control (P<0.05)].

Interpretation of the results: Levormeloxifene’s ability to inhibit elastin production in vitro, potentially through the inhibition of TGF-β1 (potent stimulant of elastin production) [2], may results in abnormal composition of extracellular matrix. Inhibition of elastin production by levormeloxifene may contribute to the development of stress urinary incontinence and prolapse.

Conclusion: Levormeloxifene increases vaginal SMC proliferation, inhibits elastin and TGF-β1 production. Levormeloxifene ability to inhibit elastin and TGF-β1 production may in part responsible for the development of incontinence and prolapse.

References