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P289. Pharmacokinetics of two monthly formulations of non-polymeric microspheres of 17?-estradiol and progesterone administered intramuscularly in an aqueous suspension in postmenopausal women

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Background: Hormonal therapy is the most effective option to manage menopausal vasomotor symptoms. Using the minimum effective dose, the non-oral route, and a natural progesterone, enhances safety.

Objective: To study the pharmacokinetics and tolerability related to the use of an aqueous suspension of non-polymeric microspheres of 17?-estradiol (E) and progesterone (P) in two formulations (E 1.0 mg/P 20 mg and E 0.5 /P 15 mg) administered intramuscularly once a month.

Methods: A randomized, open, parallel, multi-dose clinical study of pharmacokinetic characterization was carried out in healthy natural postmenopausal women. 15 women were assigned to each formulation. A total of 4 doses at 28 days intervals were administered per subject. Blood samples were obtained 7 and 3 days prior to dose 1; 0 (basal), 0.17 and 1 days after doses 1, 2 and 3; and 0 (basal), 0.06, 0.17, 0.25, 0.5, 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49 and 56 days after dose 4. E and P plasma levels were measured with a validated radioimmunoassay method. Safety was assessed by clinical evaluation, diagnostic tests and spontaneous reports of adverse events. Local tolerability was assessed by the volunteers and by physicians using a visual analogue scale.

Results: Twenty-eight women completed the study (13 assigned to E 1.0/P 20 mg and 15 to E 0.5/P 15 mg). The plasma concentration-time profile of E at steady state showed a maximum concentration of 161.54 ± 70.45 and 98.82 ± 37.20 pg/mL with doses of 1.0 and 0.5 mg, respectively. No accumulation of the preceding doses was observed. Both formulations achieved therapeutic plasma concentrations of E (>15 pg/mL) throughout the dosing interval (28 days). The minimum E concentration was 33.30 ± 21.27 and 22.06 ± 13.60 pg/mL for doses 1.0 and 0.5 mg, respectively. The maximum concentration of P was 5.27 ± 2.49 and 3.67 ± 1.54 ng/mL for doses 20 and 15 mg, respectively. Fourteen days after the injection, P levels returned to baseline with both doses. Local and systemic adverse events were transient and mild or moderate in intensity.

Conclusions Both intramuscular monthly-administered formulations of E/P non-polymeric microspheres had favorable pharmacokinetic and safety profiles; suggesting this route as an interesting and novel suitable way of treating menopausal related symptoms.

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