F046

TARGETED DRUG DELIVERY IN GYNECOLOGY: VAGINAL PROGESTERONE (P) AND THE FIRST UTERINE PASS EFFECT.

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Drugs acting on the uterus normally administered systematically may elicit adverse effects which spurred interest for local delivery systems. Recently, it has been reported that uterine tissue concentrations were higher than expected after vaginal administration despite plasma concentrations much lower than after systemic intake which led us to hypothesize some degree of direct vagina to uterus transport or "First Uterine Pass Effect". We tested this hypothesis in an human ex-vivo uterine perfusion model. Tritiated (3H) and unlabeled P mixed with freely diffusable 14C butanol were applied to the cuff of vaginal tissue remaining attached to the cervix after hysterectomy. After 1 to 12h of perfusion, 3H and 14C radioactivity were measured in uterine tissue and venous effluent. 3H water and 14C dextran were also tested to determine the non specific vagina to uterus transport (leaks). Finally, sections of uterine tissue only exposed to 3H P were prepared for autoradiography. P applied to the vaginal cuff diffused to the uterus where it was first recovered in the endocervix after 1 hour of perfusion. Later, P accumulated in the endometrium and the myometriurn and reaching a steady state after 4h with concentrations of 185 ± 155 and 254 ± 305 ng/100 mg of endometrial and myometrial tissue, respectively.

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Endometrial extraction of P was during the luteal (280 ± 156 ng/100 mg of endometrial tissue) than proliferative phase (74 ± 28 ng/ 100 mg of endometrial tissue). These data demonstrate that a "First Uterine Pass Effect" occurs when drugs are delivered vaginally thereby, explaining the unexpectedly high uterine to plasma concentration gradient observed after vaginal administration. Hence, the vaginal route permits targeting drug delivery to the uterus to maximize the desired action while limiting adverse effects. The mechanism of the first uterine pass effect has not been elucidated yet, but passive diffusion and/or counter current circulation with venous to arterial diffusion are the most likely candidates.

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VAGINAL PROGESTERONE (P) IN MENOPAUSE: LONG TERM ACCEPTABILITY OF A NEW THERAPEUTIC OPTION FOR PHYSIOLOGICAL PROGESTERONE REPLACEMENT.

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Non-oral administration of hormones is preferred when the hepatic overload inherent to oral ingestion must be avoided for medical and/or personal reasons. While estrogens can be administered transdermally, the only practical non-oral means to deliver P is transvaginally. To determine the long term acceptability of vaginal P, we conducted a retrospective analysis of our patients who received vaginal P, cyclically (10 days/month) from soft gelatin capsules originally designed for oral use. A chart review indicated that 147 menopausal and perimenopausal women 50.9±6.4 years of age had been prescribed vaginal P as part of HRT (200 mg/day, 10 days/month) over the past 6 years. Of these, 122 (83%) were available for analysis and 25 (17%) lost to follow up. Of the remaining 115 (78%) still on HRT, 20 changed for an oral progestin, 14 stopped needing P after a hysterectomy and 81 (80% of women needing a progestin) were still taking vaginal P regularly after 25.7±15.9 {6-60} months, mean±SD {interval}, in combination with oral (8.6%) or non-oral E2 (91.4%). 32% of women had switched to vaginal P after complaining of side effects with their previous medications (mood and sleeping disorders, feeling bloated, persistent hot flushes). Vaginal P was either recommended when a severe risk factor (cardiovascular or hepatic) precluded oral HRT or offered among other therapeutic options in the other cases. 28% had personal and/or familial risks of cardiovascular disease.

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12% had a familial risk of DM. 16 women smoked ≥ 20 cigarettes/day and 28 admitted to take some psychotropic and/or sleep medication. All women who did not have regular withdrawal bleeding were investigated: 2 who remained amenorrheic had cervical stenosis and 31 who presented with DUB were investigated. None had endometrial hyperplasia or cancer and most remained on vaginal P after the cause of DUB was corrected (polyp or fibroid). Side effects were rare except for a pinkish vaginal discharge linked to the capsules' dye. Women who discontinued vaginal P had remained 16.4±12 months on this therapy. In conclusion, vaginal P is well accepted for long term therapy notably, as part of HRT. The remarkable lack of systemic side effects observed with vaginal P may have played a role in the excellent HRT compliance of these patients. This opens new perspectives for improving HRT compliance through vaginal P with delivery systems especially designed for the vaginal route.