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Pharmacokinetics of HRT according to the compound and route of administration

All estrogen and progestin preparations available for hormone replacement therapy (HRT) share the common objective of providing practical and efficacious options for substituting women whose ovaries have failed. In pursuing this objective one can schematically recognize two distinct options and preferences. On the one hand, the oral route of administration follows a quest for simplicity and practicality seen as a clinical asset favoring long term compliance. As we will see, however, oral administration of hormones imposes compromises that force one to either accept mediocre bioavailability when selecting the native compound [estradiol-17β (E2) or progesterone (P)] or to use synthetic compounds that share the main biological effects of the parent (natural) hormone while resisting enzymatic degradation during the first liver pass. On the other hand, non oral administration of ovarian hormones, that appears to sacrifice simplicity, offers the advantage of giving the natural hormone (estradiol-17β (E2) or progesterone (P)) and respecting the physiological ratio between the native compound and its metabolites (E2 and estrone (E1) in the case of E2 administration ; P and its A cycle reduced metabolites in the case of progestin administration). At first glance, non oral preparations of estradiol and P may appear more complex and/or cumbersome than their oral counterparts. Yet, more often than originally thought, the lack of side effects will prove to be the best assurance for prolonged compliance.

It is the purpose of this chapter to compare the theoretical and practical advantages of the various hormone preparations and routes of administration as well as their respective advantages in selected clinical situations, particularly in women whose health is compromised such as in the case of cardiovascular disease.

Oral and non oral estrogens : the first liver pass lesson

Early follicular phase levels of E2 can be achieved with oral E2 but it takes 1 mg of E2 (approximately 15 times the daily amount produced by the ovary,

0.07 mg/24 h) to achieve similar levels. As micronized E2 is nearly entirely absorbed, the huge difference between the amount of oral E2 needed and that produced by the ovary reflects the metabolic inactivation in the bowel mucosa and liver. The practical consequences of this are two-fold : first, the liver is exposed to the entire dose ingested orally. Consequently, plasma

finding has to be borne in mind when interpreting plasma E2 values under the influence of estrogen treatments.

The physiological profile of hormone levels seen in the menstrual cycle has been duplicated with oral or transdermal E2 to optimize hormonal priming of endometrial receptivity in recipients of donor egg IVF who were prematurely deprived of their ovarian function (Schmidt et al., 1989 ; Navot et al., 1991). The E2 and P cycles designed for donor egg IVF offer an interesting model to compare oral and transdermal E2 administration. When transdermal E2 was used, women simultaneously wore a number of transdermal systems set to provide a delivery rate reproducing the physiological ovarian production pattern of E2. The profile of estradiol 17-β (E2) and estrone (E1) levels shows that E2 and E1 levels remain within the physiological range at all times. Using this model, a physiological profile of E1 and E2 levels was observed when blood samples were taken 24 to 36 h after 1 to 4 new transdermal systems (Estraderm TTS® 100) were applied (de Ziegler et al., 1991). This indicates that despite a recognized imperfection in transdermal delivery systems whereby plasma E2 levels decrease with time, levels achieved on the second day represent a proper reflection of the mean amounts of E2 delivered. Interestingly, however, despite this decrease in plasma E2 levels, no difference was observed between the two approaches in terms of endometrial effects assessed morphologically. This study also showed that transdermal administration of up 8-fold the minimal protective dose for bone preservation failed to alter levels of RS, while the latter were significantly increased by oral ingestion of minimal protective doses of E2 on bone mass (Steingold et al., 1991). The menstrual cycle profile of E2 levels could also be reproduced with oral E2 but this took 2 to 8 mg of E2 daily, resulting in markedly unphysiological levels of E1 and increasing the levels of a host of hepatic proteins (Steingold et al., 1991).

Other routes of E2 administration have been assessed such as nasal and vaginal E2 formulations :

• Intranasal 17 β-E2 administration using dimethyl-cyclodextrin as a solubilizer and absorption enhancer (Hermens et al., 1991) is characterized by very rapid E2 absorption (T_{max} below 30 min) and initial high E2 serum levels of approximately 5 nmol/L (Hermens et al., 1991). These levels quickly drop to physiological E2 levels 2 to 5 hours after administration. E1/E2 AUC-ratios are well below 1. Other nasal E2 formulations, including other cyclodextrins, are currently being assessed. The addition of progesterone to the E2 formulation does not alter the absorption or pharmacokinetics of E2 (Hermens et al., 1992).

• An intravaginal silastic ring (Estring®) releasing a very small dose of E2, 8 μg/day, over a protracted period of time (84 days) is now available in the UK (Johnston, 1996). A phase III study in 222 patients showed, at the end of one year of treatment, a mean rise in E2 of 3.9 pmol/L over a mean predose concentration of 9.8 pmol/L and a full suppression of subjective urogeni-

tal complaints (for review, see Johnston, 1996). Moreover, no change in SHBG or follicle stimulating hormone (FSH) levels were seen, which could be expected from the very low systemic E2 concentrations. This vaginal E2 administration is a promising treatment for vaginal atrophy.

Practical significance of the first liver pass of natural and synthetic estrogens

Hepatic substances can be distinguished into « friendly » substances whose increases may be seen as favorable (e.g. HDL-cholesterol), « neutral » with no foreseeable impact of their increase (e.g. SHBG and other carrier proteins) or potentially detrimental (e.g. RS). The net clinical effect of oral E2 on all these proteins is therefore an overall averaging of conflicting influences, an equation heavily affected by the dose of E2 administered. Hence, when E2 is administered orally we simultaneously induce both favorable and unfavorable substances.

The hepatic effects encountered with oral E2 are not inherently linked to the oral route of administration, but merely reflect the total amount of estrogenic effects affecting the liver. Alterations of liver proteins similar to those seen with oral E2 are also encountered when the total amount of E2 reaching the liver increases in similar magnitude without oral intake. A good example of this is provided by changes in hepatic protein levels occurring in pregnancy (de Ziegler, 1991). Soon after the establishment of pregnancy, the daily production of E2 increases tremendously above that of the menstrual cycle. Here, liver exposure is solely dependant upon plasma E2 levels. When this increases 10-20 times at the end of the 1st trimester of pregnancy the alteration of liver proteins approximates that seen with oral E2 given for HRT (de Ziegler, 1991). As the liver normally limits its exposure to E2 by metabolizing and inactivating estrogen molecules reaching the hepatocyte, increased liver exposure can also be found when synthetic estrogens such as ethinyl E2 (EE) that resist hepatic inactivation are used. Goebelsmann et al. (1985) provided a good illustration of this by studying the liver impact of vaginally administered EE. They observed that vaginally and orally administered EE had a similar hepatic impact when administered at equipotent doses. Hence, in the case of EE, the route of administration does not modify the hepatic impact, which is molecule-specific (table 15.I). Judd's group made comparable findings when studying the hepatic impact of vaginally administered conjugated equine estrogens (CE) (Mandel et al., 1983). From these two examples it can be understood that functional differences between oral and non oral estrogen treatments in terms of liver effects only exist when the natural compound, E2, is used (tables 15.I and 15.II). We will see that this principle holds true in the case of P and synthetic progestins, where it is probably more clinically relevant.

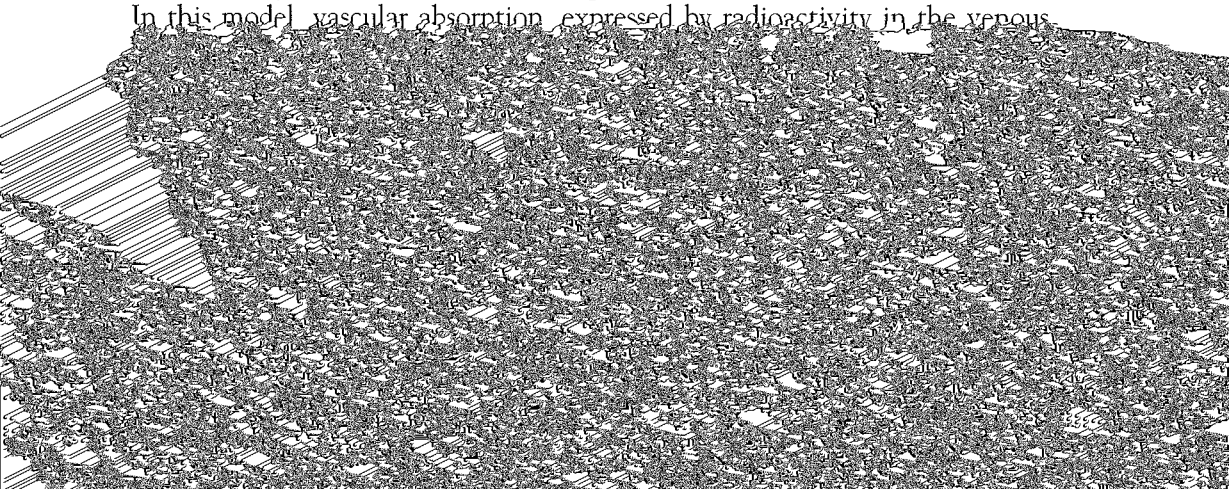
thereby explaining that oral P induces an incomplete transformation of the endometrium. In Nahoul's hands, the latter gave fairly low plasma P levels after oral ingestion of 100 mg of P. Conversely, markedly higher values were read by direct RIA methods. This difference in value readings is linked to the

effect shared with synthetic progestins and a non-genomic effect not shared by MPA (the effects of other progestins being unknown). This latter finding renders the oral - non oral dilemma much more relevant, clinically speaking, in the case of progestins.

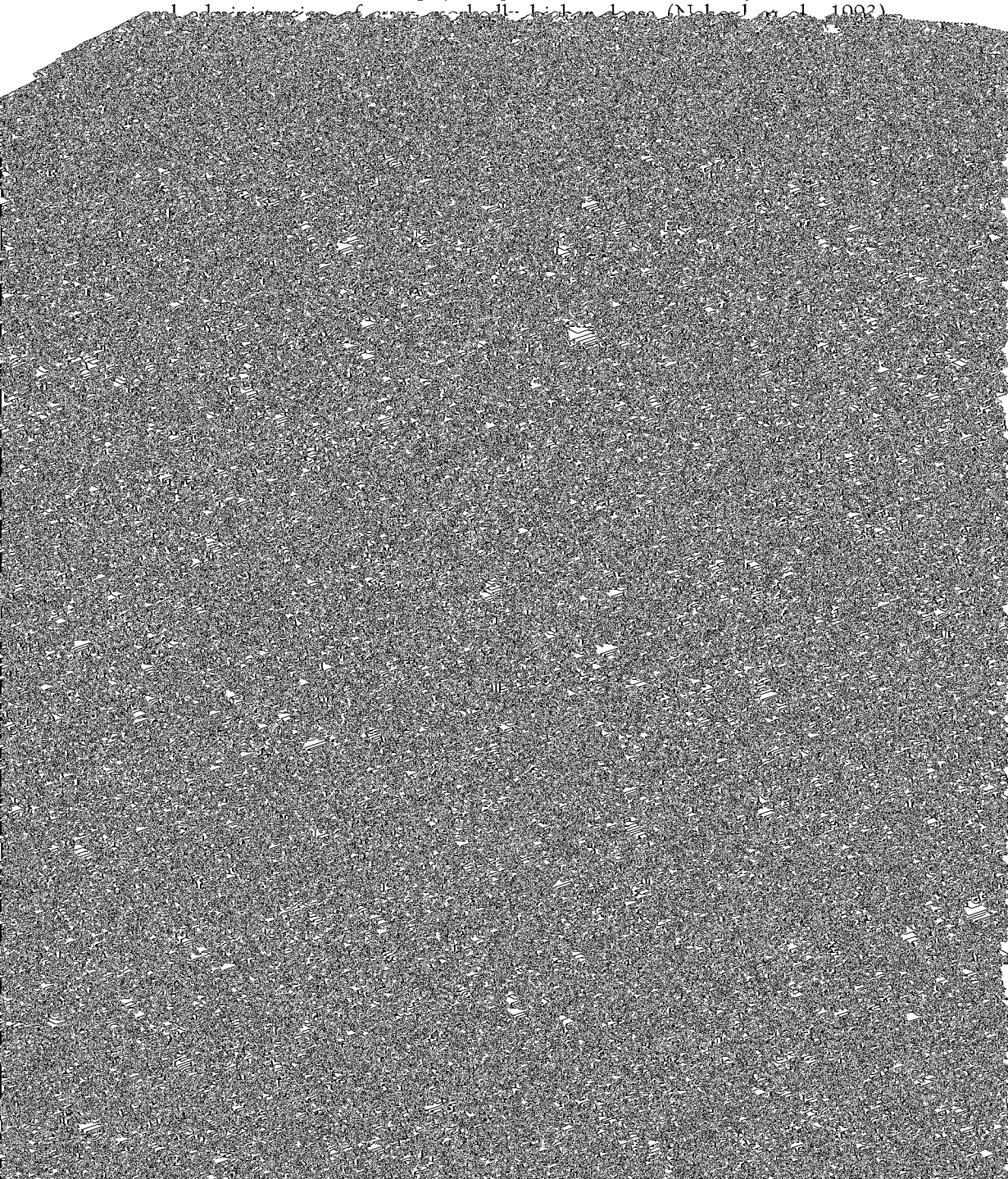
Studies with intranasal P formulations using dimethyl-β cyclodextrin (Hermens et al., 1992) or almond oil (Cicinelli et al., 1995) have shown P levels ranging from 1 to 4 ng/ml. However, endometrial effects were incomplete, particularly the transformation of the stroma which was delayed, as with administration of mini-doses of intramuscular P.

Vaginal progesterone : high efficacy linked to a uterine first-pass effect

Because the skin is poorly permeable to P, investigators and clinicians have considered the vagina as the most practical surrogate non oral route of administration. Early reports indeed indicated that vaginal P was highly efficacious at triggering predecidual changes in the endometrium and excellent pregnancy rates when used in recipients of donor egg IVF (For review, see de Ziegler, 1995). The efficacy of vaginal P became even more puzzling when we analyzed the effects of every-2-day administration of as little as 45 mg of P using the mucus-like bioadhesive vaginal gel preparation Crinone® 4 %. Plasma P levels varied between mean peak and through levels of approximately 3 and 1 ng/mL, respectively, and despite these low P levels endometrial biopsies showed full predecidualization of the endometrial stroma (Fanchin et al., 1997). The discrepancy between low plasma P levels and strong uterine effects raised the possibility that a fraction of the vaginally administered P was directly transported to the uterus through a uterine first pass effect. In support of this hypothesis is the observation by Miles et al. (1994) that vaginal P resulted in markedly higher endometrial P tissue concentrations despite lower plasma P levels. Mizutani et al. (1995) made similar findings when comparing oral and vaginal administration of Danazol. To challenge this hypothesis, the fate of vaginally administered 3H-progesterone was studied using a human *ex-vivo* uterine perfusion model (Bulletti et al., 1997). In this model, vascular absorption, expressed by radioactivity in the venous



tion) while ensuring that P levels never exceed the physiological range. Yet, these subphysiological P levels can act on extrapelvic targets, as reflected by the observed normalization of plasma gonadotropin levels (Fanchin et al., 1997). As raised earlier in this chapter, plasma P levels achieved with vaginal P administration, albeit subphysiological, are nonetheless higher than after



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