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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

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 levels of numerous hepatic substances whose synthesis is sensitive to estrogen, such as renin substrate (RS), lipoproteins (HDL-Cholesterol), sex hormone binding globulin (SHBG), steroid binding globulin (SBG) and other carrier proteins are increased when 1 to 2 mg of E2 is administered to raise circulating E2 to early follicular phase levels. Second, after oral ingestion the ratio between the parent compound and its metabolites deviates greatly from normal findings made in the menstrual cycle. A fraction of endogenous E2 released in the circulation is metabolized into E1, but the ratio of E2/E1 always remains > 1 irrespective of the E2 amount produced by the ovary. In contrast, E2 ingested orally is nearly all transformed into E1 in the bowel mucosa. E1 released into the portal circulation is further metabolized in hepatocytes, notably into E1-sulfate (E1-S), while a fraction enters the peripheral circulation. E1 is converted back into E2 in hepatic and extra hepatic sites through 17β hydroxylase. The preferential direction of this enzymatic reaction, however, accounts for circulating E1 levels that remain nearly 10-fold higher than E2. This was demonstrated for the first time by Yen`s group (Rigg et al., 1977) who took vaginal administration as model for the non oral approach. Later, studies on transcutaneous administration of E2 confirmed that physiological E2/E1 ratios are obtained when E2 is delivered non orally (Chetkowski et al., 1986).

Transcutaneous delivery of E2 encompasses two distinct approaches : first, percutaneous gels (Estrogel® or Estreva®) are based on the capacity of the most superficial layers of the skin to play the role of a drug reservoir from which E2 is released for up to 24 h towards the deeper layers and the blood vessels of the underlying dermis. The gel must be reapplied daily over a surface of skin wide enough to deliver the desired amount of E2. Second, transdermal systems of the reservoir (e.g., Estraderm TTS®) and matrix type (e.g., Systen®, Menorest®, Oesclim®, Dermestril®) release E2 at nearly constant rates for 3.5 days. Transdermal systems determine the quantity of E2 delivered per 24 h (for example, Estraderm TTS® 50 delivering 0.05 mg of E2/24h, on average for 3.5 days). In the reservoir patch, E2 is in an alcohol solution while matrix patches contain no alcohol. Comparative studies of the pharmacokinetics of these two distinct types of patches have shown that

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 vag-

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

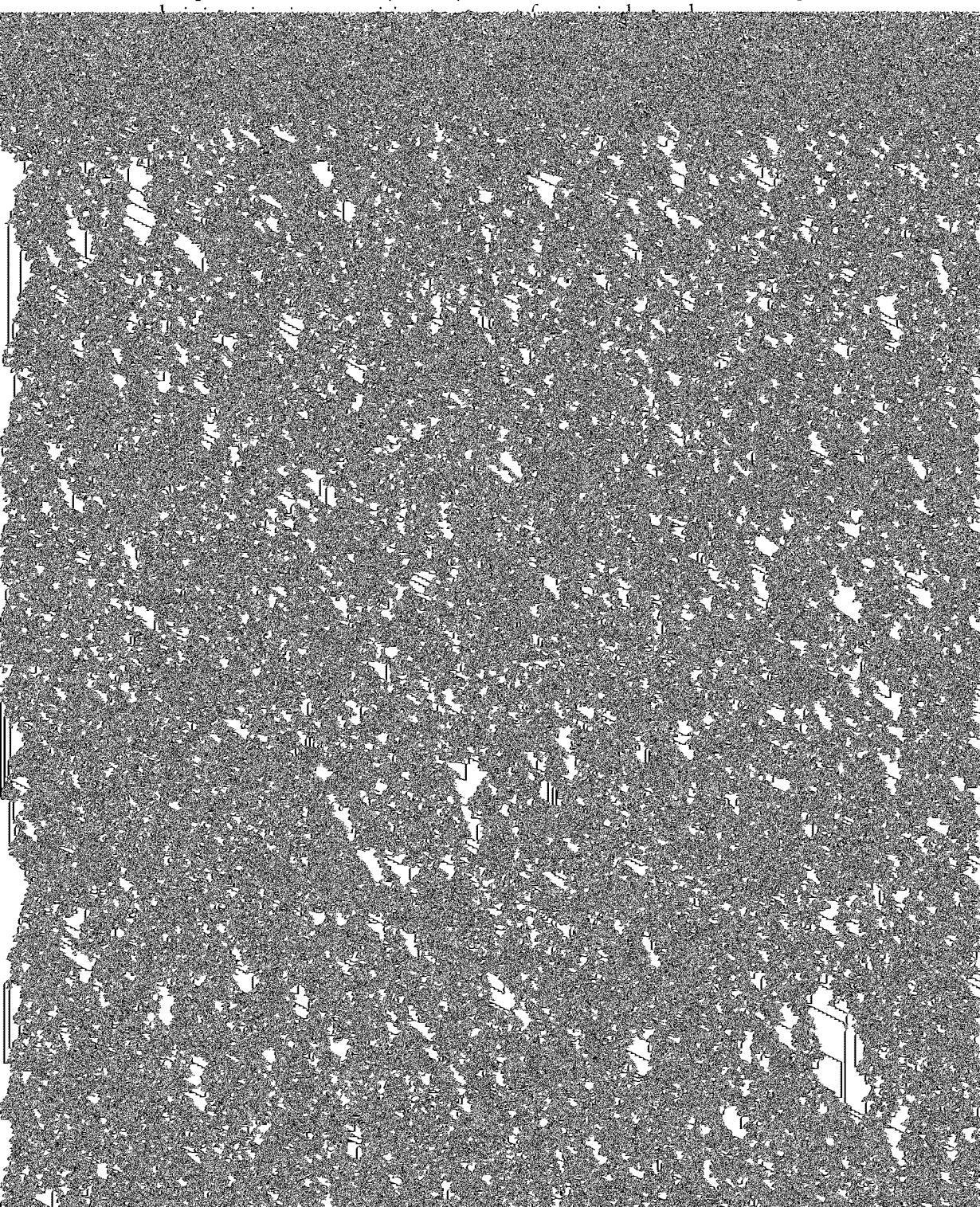


Table 15.I : HRT : Pharmacological effects on liver (I)

Route	Estrogen		
	CE	EE	E2
Oral	+	++	+
Non-oral	Vaginal	Vaginal	Transcutaneous
	+	+	0

Table 15.II : HRT : Pharmacological effects on liver (II)

Route	Molecule	
	Synthetic	Natural
Oral	+	+
Non-oral	+	0

In practical terms, there is now a body of evidence to indicate that hepatic alterations induced by the oral administration of minimal protective doses of E2 to healthy individuals have no consequences and may have some beneficial ones (increase in HDL-cholesterol). In individuals whose clinical status is compromised (e.g. in case of insulin resistance, HTA, myocardial infarction, etc.), the possibility of unwanted effects must be taken into account when selecting the treatment form. Indeed, these patients presenting with a premature high risk would probably benefit, at most, from cardiovascular protection before the age of 75 years (Jamin, 1996).

Oral progestins : progesterone and synthetic progestins

There is now ample documentation that P is absorbed after oral ingestion when micronized preparations are used. Yet, it has been impossible to reproduce the complete endometrial effects seen during the luteal phase, particularly the predecidual transformation of the stroma, despite seemingly high plasma P levels (Simon, 1995). While puzzling at first, this paradox has now been solved by a better understanding of the liver metabolism of P and its consequences on plasma determination of P by radio-immuno assay (RIA). Direct RIA for P have been validated for plasma during the luteal phase but not after oral ingestion of P. Nahoul et al. (1993) showed that this oversight was at the origin of the « high plasma levels - incomplete endometrial effects » paradox that characterized oral P. Indeed, marked differences in plasma P levels were found to be linked to the use of direct or classic extraction-separation assays. When extraction-separation assays are used, plasma P levels are only minimally elevated by oral administration of 100 mg of P,

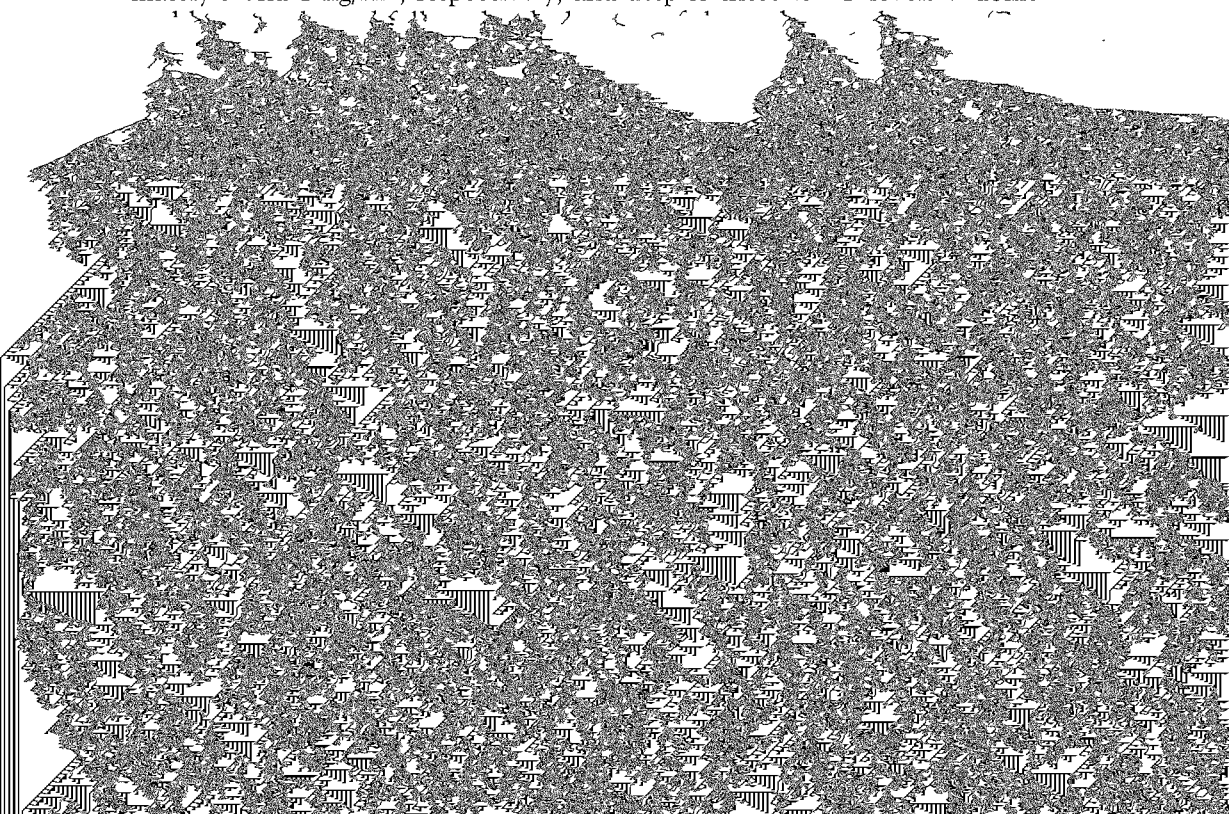
thereby explaining that oral P induces an incomplete transformation of the endometrium. In Nahoul's hands, the latter gave fairly low plasma P levels after oral ingestion of 100 mg of P. Conversely, markedly higher values were read by direct RIA methods. This difference in value readings is linked to the extremely high levels of P metabolites after oral ingestion, particularly 5b pregnanedione (not normally present in the luteal phase) and pregnanolone

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 endome-



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 oral administration of even markedly higher doses (Nahoul et al., 1993). Hence, the effectiveness of vaginal P on extrapelvic targets is no surprise.

The clinical implications of the pharmacokinetic differences between P and synthetic progestins are similar to those already discussed for estrogens. In healthy individuals, either P or synthetic progestins can be used for HRT.

To conclude, estrogens and progestins can both be administered orally and non orally. In both cases, when possible consequences are feared from the enhanced hepatic exposure linked to the first liver pass, one should prefer the natural compound E2 or P, administered non orally.

When minimal bone-preserving doses of E2 are used for HRT in healthy individuals, E2 can be administered orally or transdermally, making the selection of the treatment route a question of personal preference. One should probably be more cautious when treating compromised patients, in whom non oral E2 should be prescribed when doubts exist.

As for progestins, the use of synthetic progestins is perfectly safe in healthy individuals. Synthetic progestins, however, can be responsible for unpleasant side effects (mostly neuro-psychological) that must be recognized, as this can warrant a change from oral progestins to vaginal P. When not properly identified, the psychological and other side effects of progestins are likely to lead to the discontinuation of HRT. Clinical experience with vaginal P shows

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