15

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 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 Estraderm TTS® patch administration induced lower inter-individual variability of mean E2 concentrations and significantly ($p<0.01$) lower individual fluctuation index of E2 concentrations [defined as $(C_{max}- C_{min})/C_{mean}$] than Systen® patch administration (Jamin, 1995). Jamin also emphasized the great variability (± 400 %) of plasma E2 concentrations observed after estrogen treatments depending on the determination method (Jamin, 1995). This

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.

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. Hence, oral P has poor bioavailability, being for the most part (> 90 %) metabolized mainly into 5b reduced metabolites in the liver. One other practical consequence of the massive liver metabolism of oral P is the release of P metabolites – particularly allopregnanalone – endowed with depressing neurological properties which induce drowsiness to marked sleepiness according to individual susceptibilities.

The poor bioavailability of oral P has fueled the search for synthetic molecules sharing the effects of P but resisting enzymatic degradation so that they remained active when administered orally. The efficacy of synthetic progestins has been evaluated mainly on uterine and other markers of genomic effects of P mediated through P receptors (PR). We now know that some P effects are not genomic but rather mediated by enhancing the GABA gated Cl^- ion channel control of the cell's resting potential. This mechanism of action, identified as instrumental in the neuro-psychological effects of P, is not shared by the lead synthetic progestin medroxyprogesterone acetate (MPA) (McAuley et al., 1993). This finding explains the marked clinical differences between synthetic progestins and P in their psychological effects, the former being associated with a host of psychological effects not seen in the menstrual cycle. Moreover, there is now converging evidence that the relaxing properties of P on uterine and possibly other smooth muscles are also mediated by an allosteric activation of the $GABA_A$ receptor system by A cycle 5- reduced metabolites of P (Mahesh et al., 1996). Hence, it is plausible that the difference between the impact of P (favorable) and MPA (unfavorable) on the cardiovascular system (Adams et al., 1997) also reflects an involvement of the GABA system in the smooth muscles of the vascular wall. Our understanding of the potential importance of non-genomic effects of P would justify testing each and every synthetic progestin for these effects, as unexpected clinical differences may exist. Until then, caution is advised when treating women whose cardiovascular status is compromised.

Studies with transdermal administration of norethisterone acetate (NETA) have shown that the hepatic impact of synthetic progestins and, particularly, the possible unfavorable alteration of the lipid profile, are compound-dependent and route of administration-independent (table 15.II).

Hence, as in the case of estrogens, if the unwanted side effects of some synthetic progestins (psychological and possibly cardiovascular) are to be avoided, one should only use the natural compound, progesterone, and administer it non orally. Deviating from the paradigm seen with estrogens, however, is the unveiling of a dual mode of action for P, with a genomic

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 effluent, was rapid (1 to 2 hours). Tissue concentrations followed a different time course with progressive diffusion of radioactivity reaching the fundal area approximately 6 hours after placement on the vaginal cuff confirming the first uterine pass effect.

The vaginal route has become recognized as much more than a mere non oral mode of delivering drugs. By providing targeted delivery to the uterus, the vaginal route is ideal for delivering any substance ultimately destined to act on the uterus. In the case of P, vaginal delivery maximizes the desired effects on the endometrium (secretory transformation) and myometrium (relaxa-

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 that vaginal administration not only offers a non oral route to deliver P, but that this delivery is targeted toward the uterus by a uterine first-pass effect.

BIBLIOGRAPHY

ADAMS MR, REGISTER TC, GOLDEN DL, WAGNER JD, WILLIAMS JK. Medroxyprogesterone acetate antagonizes inhibitory effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler Thromb Vasc Biol* 1997, **1** : 217-221

BULLETTI C, DE ZIEGLER D, FLAMIGNI C, GIACOMUCCI E et al. Targeted drug delivery in gynaecology : the first uterine pass effect. *Human Reprod* 1997, **5** : 1073-1079

CHETKOWSKI RJ, MELDRUM DR, STEINGOLD KA, RANDLE D et al. Biological effects of transdermal estradiol. *N Engl J Med* 1986, **314** : 1615-1620

CICINELLI E, NAHOUL K, SABATELLI S, PETRUZZI D et al. Administration of unmodified progesterone by nasal spray in fertile women. *Gynecol Endocrinol* 1995, **9** : 289-293

DE ZIEGLER D, CORNEL C, BERGERON C, HAZOUT A, BOUCHARD P, FRYDMAN R. Controlled preparation of the endometrium with exogenous estradiol and progesterone in women having functioning ovaries. *Fertil Steril* 1991, **56** : 851-855

DE ZIEGLER D. Is the liver a target organ for estrogen? *In* : The menopause and hormonal replacement therapy : facts and controversies. R. Sitruk-Ware and W. H Utian, Marcel Dekker Inc. Publications, 1991 ; 201-225

DE ZIEGLER D, BERGERON C, CORNEL C, MEDALIE DA et al. Effects of luteal estradiol on the secretory transformation of human endometrium and plasma gonadotropins. *J Clin Endocrinol Metab* 1992, **74** : 322-331

DE ZIEGLER D. Hormonal strategies for preparing the human endometrium prior to ooctye donation. *Seminar in Reprod Med* 1995, **13** : 192-197

FANCHIN R, DE ZIEGLER D, BERGERON C, RIGHINI C, TORRISI C, FRYDMAN R. Transvaginal administration of progesterone: dose-response data supports a first uterine pass effect. *Obstet Gynecol* 1997, **90** : 396-401

GOEBELSMANN U, MASCHACK CA, MISHEL DR JR. Comparison of hepatic impact of oral and vaginal administration of ethinyl estradiol. *Am J Obstet Gynecol* 1985, **151** : 868

HERMENS WA, BELDER CWJ, MERKUS JM, HOOYMANS PM et al. Intranasal estradiol administration to oophorectomized women. *Eur J Obstet Gynecol Reprod Biol* 1991, **40** : 35-41

HERMENS WA, BELDER CW, MERKUS JM, HOOYMANS PM et al. Intranasal administration of estradiol in combination with progesterone to oophorectomized women : a pilot study. *Eur J Obstet Gynecol Reprod Biol* 1992, **43** : 65-70

JAMIN C. Protection cardiovasculaire par les œstrogènes endogènes ? exogènes ? *Le mouvement cardiovasculaire* 1996, **12** : 371-374

JAMIN C. Surveillance biologique du traitement hormonal substitutif : se fier aux dosages plasmatiques d'estradiol ou aux produits utilisés ? *J Gynecol Obstet Biol Reprod* 1995, **24** : 467-474

JOHNSTON A. Estrogens - pharmacokinetics and pharmacodynamics with special reference to vaginal administration and the new estradiol formulation - Estring. *Acta Obstet Gynecol Scand* 1996, **75** : 16-25

MAHESH VB, BRANN DW, HENDRY LB. Diverse modes of action of progesterone and its metabolites. *J Steroid Biochem Molec Biol* 1996, **56** : 209-219

MANDEL FP, GEOLA FL, MELDRUM DR et al. Biological effects of various doses of vaginally administered conjugated equine estrogens in postmenopausal women. *J Clin Endocrinol Metab* 1983, **57** : 133

MCAULEY JW, KROBOTH PD, STIFF DD, REYNOLDS IJ. Modulation of [3H] Flunitrazepam binding of natural and synthetic progestational agents. *Pharmac Biochem Behav* 1993, **45** : 77-83

MILES RA, PAULSON RJ, LOBO RA, PRESS MF, DAHMOUSH L, SAUER MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes : a comparative study. *Fertil Steril* 1994, **62** : 485-490

MIZUTANI T, NISHIYAMA S, AMAKAWA I, WATANABE A, NAKAMURO K, TERADA N. Danazol concentrations in ovary, uterus, and serum and their effect on the hypothalamic-pituitary-ovarian axis during vaginal administration of a danazol suppository. *Fertil Steril* 1995, **63** : 1184-1189

NAHOUL K, DEHENNIN L, JONDET M, ROGER M. Profiles of plasma estrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone. *Maturitas* 1993, **16** : 185-202

NAVOT D, BERGH PA, WILLIAMS M, GARRISI GJ et al. An insight into early reproductive processes through the *in vivo* model of ovum donation. *J Clin Endocrinol Metab* 1991, **72** : 408-414

POWERS MS, SCHENKEL L, DARLEY PE, GOOD WR et al. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 β-estradiol : comparison with conventional oral estrogens used for hormone replacement therapy. *Am J Obstet Gynecol* 1985, **152** : 1099-1106

RIGG LA, MILLANES B, VILLANEUVA B, YEN SSC. Efficacy of intravaginal and intranasal administration of micronized estradiol-17 β. *J Clin Endocrinol Metab* 1977, **95 :** 1261

SCHMIDT CL, DE ZIEGLER D, GAGLIARDI CL, MELLON RW et al. Transfer of cryopreserved-thawed embryos: the natural cycle versus controlled preparation of the endometrium with gonadotropin-releasing hormone agonist and exogenous estradiol and progesterone (GEEP). *Fertil Steril* 1989, **52** : 609-616

SIMON JA. Micronized progesterone : vaginal and oral uses. *Clin Obstet Gyn* 1995, **38** : 902-914

STEINGOLD KA, MATT DW, DE ZIEGLER D, SEALEY JE, FRATKIN M, REZNIKOV S. Comparison of transdermal to oral estradiol administration on hormonal and hepatic parameters in women with premature ovarian failure. *J Clin Endoc Metab* 1991, **73** : 275-280