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Pathophysiological considerations in the treatment of menopausal patients with oestrogens; the role of oestriol in the prevention of mammary carcinoma

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Abstract. At menopause, several abnormalities in oestrogen metabolism have been reported, which may increase the likelihood of cancer development in the breast or uterus following oestrone or oestradiol-17 β supplementation. Occult hypothyroidism reduces the rate of oestrogen inactivation by C2 hydroxylation, and 15-20% of women have low rates of C16 hydroxylation to oestriol. Reduced sex hormone binding globulin concentration occurs in association with obesity, thereby increasing the biologically active unbound fraction of oestradiol in plasma. Since oestriol undergoes minimal metabolism after absorption, does not bind to sex hormone binding globulin, and has an anti-oestradiol action by decreasing the duration of nuclear binding of oestradiol-receptor proteins, it is less likely to induce proliferative changes in target organs of cancer-prone women than oestrone or oestradiol. Intermittent non-conjugated oestriol treatment has demonstrated the most significant anti-mammary carcinogenic activity of 22 tested compounds as well as anti-uterotropic activity in intact female Sprague Dawley rats fed either of two dissimilar carcinogens (7, 12 dimethylbenz(a) anthracene, procarbazine) and followed for their natural life span. The protective effect was specific for mammary carcinomas only and has been decreased in rats with a 20% increase in growth curves. Clinical experience thus far with oral oestriol therapy of post-menopausal women has indicated little hazard of cancer development.

Key words: oestriol, oestrogen therapy, breast carcinoma.

Oestriol metabolism during and after the menopause is an intriguing area of endocrinology. As ovarian oestradiol and oestrone productions wane,

urinary oestradiol excretion continues at widely varying rates in different women, which reflects the parity previously experienced by each (Gross et al. 1977; Cole et al. 1976). Nulliparity enhances the risk of breast and endometrial cancer development in the years after menopause, and pregnancy completed prior to age 25 reduces the subsequent risk of breast cancer during and after menopause (Klopper & Farr 1978; MacMahon et al. 1978). The majority of investigations of urinary oestriol/oestrone + oestradiol quotients in healthy populations of pre-menopausal or post-menopausal women with varying historical risks of breast cancer development have substantiated an inverse correlation between this ratio and breast cancer risk (Table 1). Since the incidence of endometrial cancer tends to parallel the risk of breast cancer, these data may also have etiologic significance for this less frequent tumour.

A review of pre-menopausal oestrogen excretion data which have been reported over the past 20 years from healthy Caucasian women also emphasizes the wide variation in the ratio of oestriol recovered by any of several methods, to the recovery of oestrone and oestradiol (Lemon 1972). Oestriol produced in the follicular phase of the menstrual cycle is entirely derived by 16 α hydroxylation from oestrone and oestradiol secreted by the ovary, as shown by double isotope dilution studies (Barlow & Logan 1966).

During the luteal phase of the cycle when oestriol production often rises (Flood et al. 1976), 15-48% of excreted oestriol originates from non-oestrone

and duration of oestriol administration for menopausal symptoms, even though its risk of inducing breast or endometrial cancer is slight. As a result of recycling through the entero-hepatic circuit, a single dose of oestriol raises urinary oestriol excretion for as long as four days afterwards.

Since intermittent oestriol therapy appears more promising as a possible anti-mammary carcinogenic therapy than continuous therapy, we are now testing alternate day treatment with 2.5–10 mg for menopausal symptoms.

Summary

It is clear that much more needs to be learned about the oestrogen physiology of ageing women, and how one may safely increase oestrogen metabolites to improve menopausal symptomatology. Breast and endometrial cancer (and probably ovarian cancer as well) are the most feared potential complications of oestrogenic treatment. There are several lines of investigation which suggest reduced 2-hydroxylation and 16 α hydroxylation of oestrogens in women predisposed to or developing breast cancer, which are consistent with decreased mixed function oxidase activity in some women. Obesity commonly complicates menopause, providing increased extragonadal synthesis of oestrone, and in some women paradoxically decreasing sex hormone binding globulin to subnormal levels. Administration of oestrone or oestradiol would be anticipated to have excessive proliferative action on targets such as breast duct epithelium or uterine endometrium, if decreased sex hormone binding capacity were present, or reduced hydroxylation rates at the 2 or 16 carbon atom. Oestriol undergoes minimal degradation after absorption and its biologic action would not be affected either by altered mixed function oxidase activity or changes in sex hormone binding globulin; only glucuronide conjugation in the gut reduces considerably the biologic action of oestriol, which can be avoided by intravaginal administration. Unconjugated oestriol has demonstrated anti-mammary carcinogenic activity in intact female rodents against two dissimilar chemical carcinogens, supporting the epidemiologic thesis which has developed, indicating an inverse relationship between urinary oestriol excretion relative to oestrone and oestradiol in human populations and

breast cancer risk. This inverse correlation may fact reflect how early in maturity pregnancy is permanently induced increased 16 α hydroxylation of oestradiol or adrenocortical precursors of oestriol to increase the production of this physiologic anti-oestradiol antagonist in some women.

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