Letter to the Editors

Is the use of conjugated equine oestrogens in hormone replacement therapy still appropriate?

Conjugated equine oestrogens (CEE) have been used for several decades for postmenopausal hormone replacement. The preparation is in the form of an extract from the urine of pregnant mares containing the effective substances, i.e. oestrogen metabolites. This was one of the earliest commercial preparations available for postmenopausal hormone replacement. Treatment with extracts of biological material has become less common nowadays because it is difficult for them to fulfil the high specifications for pharmacological products. The preferred aim now is the use of monosubstances with clearly defined pharmacokinetic and pharmacodynamic features.

There are many uncertainties in the characterization of CEE. The British Pharmacopoeia, Martindale, which in general provides comprehensive information on drugs, gives little data on CEE [1]. It is known that the preparation contains oestradiol metabolites as well as equilin metabolites which are specific to horses. However, there is still a dearth of knowledge about the exact components of the urine extract. Hitherto unidentified components have been recognized recently in the extract [2]. These are delta-8-oestrone and its metabolites; furthermore 16α-hydroxy metabolites and catechol metabolites of equilin are also allegedly present. The pharmacological properties of these substances are still largely unknown and it is likely that other, previously unidentified steroids are also present.

It is now known that oestrogen metabolites possess effects other than their oestrogenicity [3]. Thus, some have opposing effects: for instance, D-ring metabolites may exert proliferation-stimulating effects on cells, but A-ring metabolites proliferation-inhibiting effects. In general, D-ring metabolites still have an oestrogenic effect, while A-ring metabolites may even show antioestrogenic effects. There has been recent interest in oestrogen metabolites because there are indications that they can be involved in the development of hormone-dependent tumours, e.g. breast cancer [3]. Zhang *et al.* have shown that equilin metabolites have toxic properties with carcinogenic potential through the formation of quinones [4]. A special carcinogenic risk factor may be the formation of semiquinone-adducts with DNA [5].

Equilin metabolites appear to have stronger carcinogenic effects than comparable oestradiol metabolites [2]. In the 1980s, Diczfaluzy [6] expressed the view that it was not only the quantatively dominant metabolites that were important but probably also those less frequently present. There is still need for information in this field.

It is long-term therapy with hormone replacement (HRT) that causes most concern in relation to the development of breast cancer. Because CEE has been available for longer than most other preparations, it predominates in the majority of studies which have shown this connection. This emphasizes the importance of establishing exactly what substances with carcinogenic potential are contained in the extract. It cannot be assumed that other HRT preparations share the same potential for an increase in associated breast cancer with long-term use.

Because the extract from mares' urine contains equilins that occur only in horses and are a foreign substance for humans, the description 'natural oestrogens' is really not correct. Also, the claim that the CEE extract exerts its positive effects by virtue of its mixture of components has no scientific basis [2]. The overall effect on postmenopausal women may be the resultant of different, partly competing, effects of metabolites and the effect of individual components may be masked.

Oestradiol is now available in pure form, crystalline or as oestradiol valerate, and it seems more sensible to replace the oestradiol deficiency by giving the exact hormone rather than an extract of uncertain composition. Since CEE offers no advantage over physiological oestradiol, it is hard to understand why substitution with a pharmacologically poorly defined oestrogen mixture is still practised. From the point of view of clinical pharmacology, the use of an oestrogen extract should now be considered inappropriate.

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