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Sublingual delivery of 17β-estradiol from cyclodextrin containing tablets

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17β-Estradiol is a rather lipophilic water-insoluble drug (log octanol/water partition coefficient (log $K_{o/w}$) 2.58; solubility in water 0.1 mg/ml) [1, 2]. The drug is well absorbed from the gastrointestinal tract but due to first-pass effect its bioavailability after oral administration is only about 5%. It is possible to enhance the bioavailability of 17β-estradiol by nasal, transdermal or sublingual administration [3–6]. Drug absorption from the oral cavity through the lipophilic mucosal membrane is a function of the surface area, permeability coefficient and the concentration of dissolved drug at the surface of the membrane [7]. The available surface area is relatively small or about 100–170 cm^2 and it is covered by an aqueous salivary film 0.07 to 0.10 mm thick. Thus the drug must be water-soluble to be able to permeate to the membrane surface and somewhat lipophilic to be able to permeate the lipophilic mucosal membrane. Cyclodextrins are relatively large hydrophilic molecules (MW ranging from about 1000 to over 2000) that form water-soluble complexes with many lipophilic drugs. They do not readily penetrate lipophilic biomembranes such as mucosal membranes. Studies have shown that cyclodextrins enhance drug delivery through lipophilic biological membranes by increasing the amount of dissolved drug molecules at the membrane surface. At the surface the drug molecules partition from the complex into the outermost layer of the membrane [8]. Thus cyclodextrins are able to increase the aqueous solubility of β-estradiol without reducing its ability to permeate the lipophilic mucosal membrane.

Previously, we have shown that 2-hydroxypropyl-β-cyclodextrin (HPβCD) forms a water-soluble complex with 17β-estradiol and that the complex is able to deliver the lipophilic water-insoluble drug to the lipophilic membrane surface [3]. The purpose of the present study was to evaluate sublingual tablets containing 50 and 100 μg of 17β-estradiol in a HPβCD complex.

Sublingual tablets containing 17β-estradiol/HPβCD complex, equivalent to 50 and 100 μg 17β-estradiol, were given to five postmenopausal women in an open crossover study and the estradiol plasma levels determined up to 12 h after administration (Fig.). The drug was rapidly absorbed with maximum plasma concentration (C_{max}) appearing within 15 to 30 min and terminal half-life ($t_{1/2}$) of about 3.5 h (Table). When compared to values obtained by Devissaguet et al. [4] it appears that 17β-estradiol is more rapidly (somewhat shorter t_{max} and larger C_{max}) absorbed after nasal administration. However, nasal administration of drugs has been associated with large individual variations and pathological changes in the nasal mucosa [9]. The present study shows that systemic delivery of 17β-estradiol from the buccal area is possible through cyclodextrin complexation of the drug. The sublingual drug delivery has many of the advantages of the nasal drug delivery but it is in general more reliable, less irritating and more convenient, which all leads to better patient compliance.

Table: Mean pharmacokinetic parameters of 17β-estradiol following sublingual and nasal administration

Parameter	17β-Estradiol (dose μg)		
	Sublingual		Nasal[a]
	50	100	100
C_{max} (pmol/L)	400 ± 45	1084 ± 243	2560 ± 1020
t_{max} (h)	0.50	≤0.25	0.17
$t_{1/2}$ (h)[b]	–	3.5	2.7

a From reference [4]
b The elimination half-life of exogenous 17β-estradiol

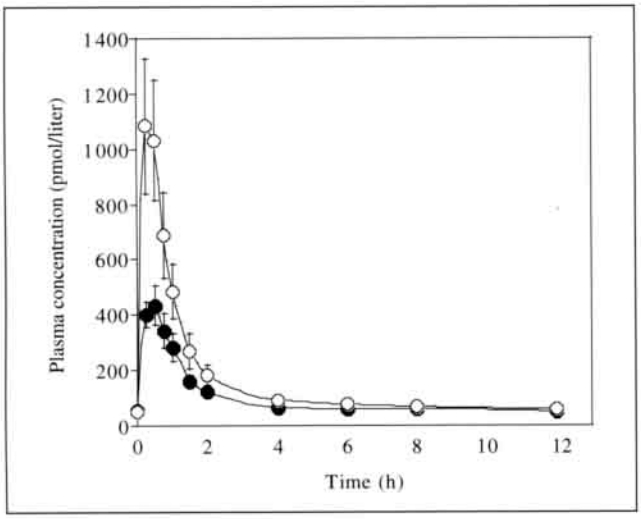

Fig.: Mean plasma concentrations of 17β-estradiol after administration of sublingual tablets containing 100 μg (○) and 50 μg (●) of 17β-estradiol. The error bars represent the SEM (n = 5)

Experimental

One or two grams of 17β-estradiol were dissolved, through heating in an autoclave to 120 °C for 20 min, in an aqueous 50% (w/v) HPβCD solution containing 0.25% (w/v) CMC [3]. The solution was then lyophilized in a Snijders lyophilizer (the Netherlands). Quantitative determinations of 17β-estradiol in the complex powder were performed by HPLC. The lyophilized complex was mixed with lactose, crospovidone, silica colloidalis and magnesium sterate. The tablets were directly compressed in a rotary tablet press (Stokes-Merrill, USA) using 6 mm punches with a target weight of 86.0 mg and disintegration time of less than 1 min. Five postmenopausal women (50 to 65 years old, 52 to 77 kg) were recruited for an open study. All the women were inpatients of the Department of Obstetrics and Gynecology, University Hospital, Reykjavik. The study was approved by the local ethical committee and the Ministry of Health. All the women volunteers signed an informed consent form. Before treatment, low endogenous 17β-estradiol production was confirmed by measurement of FSH levels. The women received single doses of 50 or 100 μg 17β-estradiol in a buccal tablet. Blood samples were withdrawn over a period of 12 hours and the 17β-estradiol concentration determined by time-resolved fluoroimmunoassay (DELFIA) with reagents from Wallac, Finland. The detection limit was better than 50 pmol/l.

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