

17 α -Ethinyl estradiol

Synonym: 17 alpha-ethinyl estradiol

CAS number: 57-63-6

MF: C₂₀H₂₄O₂

MW: 296.4

Solubility: lipophilic compound; easily dissolved in fat-like (e.g. hydrocarbon) compounds; not soluble in water.

Major use

17 α -ethinyl estradiol (EE) is a potent synthetic estrogen (estradiol). It is used as an oral contraceptive, or the component of the synthetic estrogen, 17 alpha-ethynylestradiol-17 beta. Usually, the concentration of EE in contraceptive tablets is 20 to 35 μ g (often in a combination with other steroid hormone).

Human toxicity

Generally, estrogens are of low order of toxicity. After acute overdosage, gastrointestinal symptoms such as nausea, vomiting, abdominal cramps, diarrhea, and headache may occur [1].

The therapeutic daily doses of estradiol are in the range of 0.05-1 mg per day [2]. In some cases doses about 0.15 (0.1-0.2) mg may be regarded as toxic [3].

The therapeutic blood concentration of estradiol is in the range of 0.000095-0.00016 mg/l [3].

In two acute poisoning cases, the toxic (sub-lethal) blood concentration of estradiol was 0.00057 and 0.00085 mg/l, respectively [4].

Carcinogenicity: estrogens are not classified as human carcinogens. However, increased relative risk of endometrial carcinoma and breast cancer has been associated with prolonged medical treatment [1].

Kinetic data

Absorption is rapid and generally complete [2].

Distribution: estrogens are widely distributed throughout most body tissues with the greatest concentration in fat deposits. Rapid transfer between fetus and mother was demonstrated [5].

Protein binding: 50 to 80% [5]. EE is bound extensively to serum albumin [2].

The elimination half-life has been reported in various studies to be 13 to 27 h [2].

Metabolism and excretion

The metabolic fate of synthetic estrogens has not been fully determined. Estradiol is metabolized primarily in the liver; metabolism also occurs in the kidneys, gonads, and muscle tissue.

The primary route of biotransformation of EE is via 2-hydroxylation and subsequent formation of the corresponding 2- and 3-methyl ethers. The major human catalyst of the 2-hydroxylation reaction is liver microsomal cytochrome P450 IIIA4 [6].

Endogenous estrogens appear in the urine as glucuronides and sulfates of estradiol, estrone, and estriol [2].

Estrogens slightly elevate serum triglycerides and slightly reduce total serum cholesterol level [2].

Excretion: The primary route of excretion is via urine. The steroids and their metabolites are conjugated which increases their water solubility and facilitates excretion into the urine [2].

Pharmacological mechanisms

Most of the known actions of natural (naturally occurring estrogen in humans is 17 β -estradiol) and synthetic estrogens can be regarded as physiological, e.g. their regulation effects on sexual development in females, neuroendocrine control of the menstrual cycle, regulation of implantation by induction of progesterone receptor etc. Generally, the contraceptive effects of estrogens are associated with their ability to decrease the amount of follicle stimulating hormone and luteinizing hormone, which are important for the preparation of the uterus to implantation if the ovum is fertilized [2].

The ethinyl substitution at the C 17 position in estrogen greatly increases its contraceptive potency by inhibiting first-pass hepatic metabolism (especially 2-hydroxylation) [2, 6].

Target organs: gastrointestinal tract; also liver, when the therapeutic doses were applied at prolonged medication [2].

References

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2. Goodman Gilman, A., Rall, T.W., Nies, A.S., Taylor, P., eds. (1996). *The Pharmacological Basis of Therapeutics*. 9th ed., McGraw-Hill.
3. Persson, H. & Sjöberg, G. (2006) Överdosing av läkemedel (Overdose of Drugs). In FASS (Drugs in Sweden). Stockholm: Linfo.
4. Fracog, J.E. (1990) Too much of a good thing? Two cases of oestrogen overdose associated with oestradiol implants. *Med J Australia* 152, 558.
5. AHFS, Drug information Web Site (Internet, via Google).
6. Guengerich, F.P. (1990) Metabolism of 17 alpha-ethynylestradiol in humans. *Life Sci* 47(22):1981-1988.

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