Maturitas 72 (2012) 108–112

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Diethylstilboestrol—A long-term legacy

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ARTICLE INFO

Article history:
Received 1 March 2012
Accepted 4 March 2012

Keywords:
Cancer
Diethylstilboestrol
Endocrine disrupter
Epigenetics
Steroid

ABSTRACT

Diethylstilboestrol (DES) is an endocrine disrupter which causes cancer in rodents. It was prescribed in large amounts to treat women with gynaecological problems; some of the daughters of these women subsequently developed a rare cancer (vaginal clear cell adenocarcinoma) while genital abnormalities were found in some of the sons. It was used for decades in livestock feed and this may have contaminated the food chain leading to the exposure of the more general population. DES appears to cause epigenetic effects in animals and there is some evidence that this also occurs in man. The mechanisms of carcinogenesis are complex and the effects are difficult to prove due to the background of dietary and environmental phyto- and xenooestrogens. It has been suggested that, like other endocrine disrupters, DES may have acted as an obesogen in the human population.

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1. Introduction

It has been said that, "the road to hell is paved with good intentions," and this aphorism might well be applied to diethylstilboestrol (DES). In an attempt to prevent miscarriages caused by progesterone deficiency [1], between 1940 and 1971, DES was prescribed to several million pregnant women. Today, concern about minute amounts of endocrine disrupters in the diet frequently borders on the hysterical, but at the time the potential consequences of dosing hundreds of milligrams of a powerful synthetic oestrogen were simply not anticipated. Now, forty years after its prescription was banned, its legacy may continue to affect not only mothers and children but also grand children.

2. DES in animals

If DES were to be introduced under modern regulations it would never get past the first post. It causes tumours in several animal species at several different tissue sites that are usually oestrogen sensitive. Prenatal exposure caused both benign and

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doi:10.1016/j.maturitas.2012.03.002

malignant cervical, vaginal and uterine tumours in female hamsters and female mice and benign lung tumours in mice of both sexes [2]. Male hamsters developed malignant testicular tumours when exposed prenatally and male rats developed squamous-cell carcinomas of the reproductive system after daily subcutaneous injections for the first 4 weeks of life. Rodents may be more sensitive to the effects of DES as prenatal exposure did not cause tumours in monkeys even 6 years after birth [2].

DES also caused cancer in adult rodents when dosed orally. Mice of both sexes developed mammary gland carcinoma while female mice also had cancers of the cervix, uterus and vagina [2]. Bone tissue can be oestrogen-responsive and osteosarcomas were also seen in mice while orally dosed rats developed pituitary gland and liver tumours as well as cancers of the reproductive system. Subcutaneous injections of DES in mice increased the incidences of leukaemia and lymphoid tissue tumours as well as those of the reproductive system while rats developed bladder cancers as well as adrenal tumours and the expected reproductive system tumours, which were also seen in dogs and squirrel monkeys [3].

Several multi-generation reproductive toxicology studies were carried out. When mice were exposed to DES *in utero*, just before birth or just after birth and the females (F_1) were then raised to maturity and mated with unexposed males, the F_2 generation had increased incidences of reproductive tract tumours; the females developed uterine cancer while the males developed cancers of the seminal vesicles and sperm-carrying tubules [4].

3. DES in human therapy

The synthesis and oestrogenic properties of DES were first reported by Dodds et al. in February 1938 [5]. The molecule has a similar shape to oestradiol to which it bears a much closer resemblance than bisphenol A (Fig. 1). DES was never patented and by the end of 1941 the Food and Drug Administration had established a generic formulation approved for use in the United States. In 1948 Smith published a paper on the use of DES in the prevention and treatment of complications of pregnancy [1]. Only a small section of the paper expressed concern about the theoretical dangers of using unphysiological amounts of oestrogens. Nevertheless, DES was routinely prescribed until 1971 to treat cases of threatened miscarriage in the first trimester. It was also used to treat prostate cancer and breast cancer in post-menopausal women; to inhibit lactation; to control abnormal gynaecological bleeding [6]; and to stunt the growth of girls who were predicted to grow 'abnormally tall' [7]. Quite large doses were sometimes used—in one large cohort, the median total doses ranged from 1.625–10.424 g [3]. Estimates in America suggest that between 5 and 10 million people either received the drug in pregnancy or were exposed *in utero*, while corresponding numbers in the UK may be around 300,000 and about 200,000 in France although many patients were never told that they had been prescribed DES, these numbers are only approximate.

Problems were first highlighted in 1953 when it was clear that not only was DES ineffective during pregnancy but it might actually be slightly detrimental [8]. However, a powerful and emotive advertising campaign ensured that its use continued until 1971 when Herbst et al. [9] showed that DES appeared be the cause of an increased incidence of vaginal clear cell adenocarcinoma (CCA) in the daughters of women treated with the drug. The US Food and Drug Administration (FDA) issued a drug bulletin in that year, advising physicians to stop prescribing DES because of the link to this cancer. In 1978 the FDA withdrew approval for the use of DES for suppression of post-partum lactation and breast engorgement. Despite the information that DES was a human carcinogen operating by a previously unknown mechanism, it continued to be used

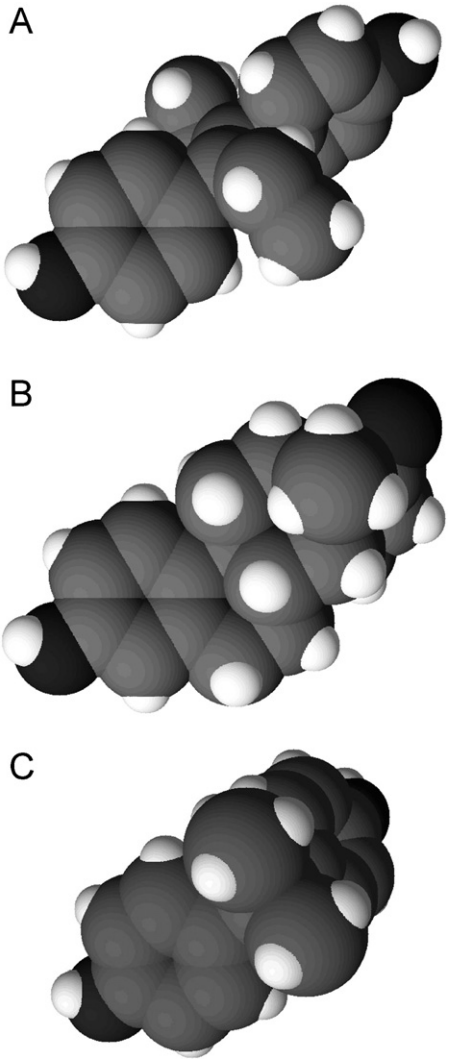

Fig. 1. Space-filling representations of (A) diethylstilbestrol; (B) oestradiol; (C) bisphenol A.

in clinical trials for treatment of prostate and breast cancer until the late 1990s.

Studying the effects of DES on humans is complicated by two factors. Firstly, DES undergoes complex metabolism involving both cytochromes P450 [10] and sulphotransferases [11]; both of these enzyme systems are modulated by xenobiotics including food, drugs and environmental contaminants [12,13]. Secondly, many of the effects of DES are duplicated by other endocrine disrupters including phytoestrogens. For example, boys born to mothers who follow a vegetarian diet during pregnancy are more likely to suffer from hypospadia [14]. Consequently, it is difficult to isolate relatively subtle effects epidemiologically and it was only the rarity of vaginal adenocarcinoma that enabled Herbst et al. to identify DES as the causative agent.

4. DES in animal feed

Hormonal status was known to influence feed conversion and the efficiency of production of lean meat so DES was soon used in cattle and chickens. In 1947, experiments at Purdue University, using DES implants (42–48 mg) showed that treated heifers had improved weight gain (~15%) and feed conversion but showed vulvar swelling and extended oestrus. The meat was leaner but of reduced quality; lower doses of 30–36 mg were later used