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SCIENCE DIRECT
Epilepsy & Behavior 9 (2006) 31–39
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Review

The impact of antiepileptic drug therapy on steroidal contraceptive efficacy

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Received 23 January 2006; revised 1 May 2006; accepted 3 May 2006
Available online 12 June 2006

Abstract

Women with epilepsy face unique challenges in maintaining steroidal contraceptive efficacy because some antiepileptic drugs (AEDs) increase the rate of hepatic metabolism of contraceptive steroids, leading to higher potential for contraceptive failure in this population. Planned pregnancy is of great clinical and social importance for women with epilepsy because of the increased risk of birth defects from fetal exposure to AEDs. Current clinical guidelines for contraceptive management in women with epilepsy provide misleading information by focusing on the estrogen content of the formulation, which regulates the menstrual cycle, rather than on the progestin content of the formulation, which provides contraceptive efficacy. This article reviews studies of AED–contraceptive interaction and misconceptions about maintaining contraceptive efficacy and makes recommendations for contraceptive management in women with epilepsy who receive concomitant AED therapy.

Keywords: Antiepileptic drugs; Contraception; Efficacy; Enzyme induction; Epilepsy; Treatment guidelines; Hepatic metabolism; Steroidal contraceptives; Women

1. Introduction

Women with epilepsy who are treated with antiepileptic drugs (AEDs) face unique challenges in contraception. Certain AEDs can induce hepatic metabolism of steroidal contraceptives (SCs), leading to decreased contraceptive efficacy. However, several surveys suggest that a large percentage of health care professionals have limited knowledge about optimizing contraceptive efficacy in female patients with epilepsy [1,2], that women of reproductive age who are treated with enzyme-inducing AEDs do not receive information about potential drug interactions [3], and that women who take AEDs have a high oral contraceptive (OC) failure rate [1].

Although more than 90% of women taking AEDs during pregnancy will deliver a healthy child, 4–7% of fetuses exposed to certain AEDs are at increased risk of having birth defects [4]. Therefore, contraceptive efficacy is a major concern for women with epilepsy. A lack of confidence in the method of contraception can lead to detrimental psychosocial stresses, including decreased sexuality and fear of teratogenesis [5]. Women with epilepsy desire treatment that offers optimal seizure control together with reliable birth control, healthy pregnancies, and healthy children [6]. Good counseling and pregnancy planning are essential to achieving these goals.

This article reviews the published literature addressing AED–contraceptive interaction, discusses misconceptions

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doi:10.1016/j.yebeh.2006.05.002

in current contraception management in women with epilepsy, and offers recommendations on reliable contraception methods for women to use concomitantly with AEDs.

2. Current contraception guidelines for women with epilepsy: Flaws

Current guidelines for contraceptive use by women with epilepsy suggest that contraceptive efficacy is provided by the estrogen component of these agents [7,8]. In fact, it is the progestin component of SCs that provides contraceptive efficacy [9,10].

For example, the Commission on Genetics, Pregnancy, and the Child, International League Against Epilepsy guidelines for the care of women of childbearing age with epilepsy suggest that breakthrough bleeding is a sign of contraceptive failure that is due to low estrogen dosage resulting from possible interaction between AEDs and SCs [7]. The American Academy of Neurology (AAN) Practice Parameters recognize that the risk of contraceptive failure may be increased as bioavailable estrogen and progestin are reduced by the use of those AEDs that activate isozymes of hepatic cytochrome P450 (CYP450) or increase production of steroid hormone-binding globulins (SHBGs). AAN guidelines recommend that the contraceptive formulation contain at least 50 μg of ethinylestradiol or mestranol to control breakthrough bleeding [8]. Neither set of guidelines makes recommendations for progestin dosage.

Although the available guidelines recognize that some AEDs can reduce the efficacy of SCs, they provide flawed guidance for providing effective contraception. Although estrogen levels are reduced by the action of enzyme-inducing AEDs, it is the progestin component of the contraceptive that prevents ovulation. Current guidelines omit this crucial information.

3. Steroidal contraceptive mechanism of action

During the first stage of the menstrual cycle (follicular phase), the hypothalamus produces gonadotropin-releasing hormone (GnRH). GnRH stimulates the pituitary gland to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH), causing follicles to mature ovarian. Pituitary FSH secretion drives the production of estrogen, which gradually increases throughout the follicular phase. Just before ovulation, the negative feedback of estrogen on pituitary LH/FSH changes to positive feedback. This produces a surge in LH, as well as a surge in estradiol, which causes release of the oocyte from the follicle in the ovary into the fallopian tubes (ovulation). In the second stage of the menstrual cycle (luteal phase), the granulosa cell remnants of the follicle form the corpus luteum, which secretes large quantities of progesterone and, to a lesser degree, estradiol in response to LH. These hormones prepare the endometrium for implantation of the fertilized egg. If fertilization does not occur, production of estrogen and progesterone decreases, and menstruation begins [11].

In the 1950s, the initial development of SCs was based on the observation that progesterone is responsible for the suppression of ovulation. In early tests of contraceptives, the use of impure progestogen samples provided evidence that estrogen was necessary for menstrual cycle regulation [12]. Analysis of bleeding patterns in women using a number of contraceptive modalities has confirmed the necessity of estrogen for proper cycle control [13]. Progestin-induced irregular menstruation may provide misleading evidence of altered hormone cycling due to pathology [14]. Therefore, scheduled endometrial shedding brought about by the oral intake of estrogen may contribute to psychological well-being as well as convenience.

Currently, SCs contain either a combination of synthetic estrogen and synthetic progesterone-like steroid or a single synthetic progesterone-like component (Fig. 1) [15]. Typically, the synthetic estrogen component of combined SCs comprises either ethinylestradiol or mestranol. Ethinylestradiol is an orally active derivative of the endogenous hormone estradiol, with the addition of an ethinyl group to the pentane ring. Mestranol is essentially ethinylestradiol with a methylated hydroxyl group on the benzene ring. The progesterone-like component of either combined or single-agent contraceptives comprises one of a variety of synthetic progestational steroids called progestins or progestogens, which are similar in structure to the native hormone progesterone. Norethindrone, for example, differs from progesterone by the lack of a methyl group at position 6 and the substitution of a hydroxyl group and an ethinyl group for the ketone at position 17. Levonorgestrel differs from norethindrone by the substitution of an ethyl group for the methyl group at position 13 [16,17].

Progestins induce four discrete contraceptive processes in the body. First, they inhibit production of GnRH by the hypothalamus. The reduction in GnRH limits production of LH and of FSH by the pituitary gland, thereby suppressing the midcycle pulses of LH necessary to initiate ovulation (Fig. 2) [18]. Second, progestins cause cervical mucus to thicken, which blocks the passage of sperm. Third, they cause the endometrium to atrophy, making it unsuitable for ovum implantation. Fourth, they limit fallopian tube cilial motility, preventing the timely transport of the ovum to the uterus [9,19].

The estrogen component of combined SCs plays two important physiologic roles. First, estrogen augments the effects of progestins by increasing the concentration of intracellular progestin receptors. Estrogen also suppresses the release of FSH from the pituitary, further inhibiting the emergence of a dominant follicle. Therefore, estrogen may contribute indirectly to the efficacy of combined SCs. Second, and more importantly, estrogen stabilizes the endometrium, minimizing breakthrough bleeding and unscheduled endometrial shedding, which increase patient satisfaction and compliance [10].