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Original research article

Co-prescription of antiepileptic drugs and contraceptives☆

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Abstract

Background: Enzyme-inducing antiepileptic drugs (AEDs) reduce the efficacy of oral contraceptives. Little is known of contraceptive practice among reproductive-age women who receive AEDs.
Study Design: We explored the use of contraceptive methods among Dutch women aged 15 to 49 years with prescriptions of AEDs using pharmacy dispensing database. Drug dispensing data of AEDs and contraceptives in 2006 was retrieved from the InterAction Database (IADB.nl database). The prevalence of contraceptives use and distribution of different contraceptive methods were calculated.
Results: Of women who used enzyme-inducing AEDs in combination with any highly effective contraceptive method, over 40% were on an oral contraceptive (OC) containing <50 mcg estrogen. IUDs and injectable contraception were used in 22.5% of women receiving AEDs in combination with any highly effective contraceptive method, and 33.2% in those receiving enzyme-inducing AEDs in combination with any highly effective contraceptive method.
Conclusion: Fertile-age women who received AEDs often relied on less effective contraceptive methods. Prescribers should be more aware of the interaction between AEDs and OCs.
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Keywords: Antiepileptic drug; Enzyme inducing; Contraceptive; Women

1. Introduction

Epilepsy affects 0.5-1.0% of the population. About half of these are women, many of childbearing age. Co-administration of oral contraceptives (OCs) and antiepileptic drugs (AEDs) is a common clinical situation which calls for specific considerations of possible drugs interactions. Some AEDs, i.e., the enzyme-inducing AEDs, induce cytochrome P450 hepatic enzyme activity which increases the rate of metabolism of both estrogen and progestrogens, and thus lower the blood levels of these hormones [1]. The main consequences of these interactions are increased risk of unintended pregnancy. Given the increasing evidence of the teratogenic effects of some AEDs [2], contraceptive efficacy is of greater concern for women treated with AEDs than for women in the general population. The usual OC containing <50 mcg of estrogen is susceptible to a lower hormonal effect by AED interaction, resulting in contraceptive failure. Epileptic women treated with enzyme-inducing AEDs should be advised to use an OC containing at least 50 mcg of estrogens [3]. There is little published information on contraceptive prescribing patterns for women of childbearing age who use AEDs. A UK study using the general practice research database reported that 56% of epileptic women using both enzyme-inducing AED and an OC, took a low dose estrogen OC [4]. However, only OCs were included in this study. The present study explored the choice of highly effective contraceptive methods, including intrauterine device (IUD) and injectable contraception among Dutch women who were prescribed an AED, compared with women in the general population.

2. Methods and materials

This study was performed using the InterAction Database (IADB.nl database) (http://www.IADB.nl), a longitudinal pharmacy dispensing database in the northern Netherlands with detailed patient-based drug prescription information. The procedures and sources of data have been documented [5,6]. Briefly, the IADB.nl database comprises all pharmacy

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Table 1
Antiepileptic drugs in the IADB.nl in 2006

Enzyme inducing-antiepileptic drugs		Non-enzyme-inducing antiepileptic drugs	
Name	ATC-code	Name	ATC-code
phenobarbital	N03AA02	ethosuximide	N03AD01
primidone	N03AA03	clonazepam	N03AE01
phenytoin	N03AB02	valproic acid	N03AG01
carbamazepine	N03AF01	vigabatrin	N03AG04
oxcarbazipne	N03AF02	gabapentin	N03AX12
felbamate	N03AX10	levetiracetam	N03AX14
topiramate	N03AX11	pregabalin	N03AX16
lamotrigine	N03AX09		

ATC-code: Anatomical Therapeutic Chemical code.

prescriptions from approximately 500,000 persons during 1998-2007 and is considered representative of the Dutch population in terms of drug use. Commitment of people to their pharmacy has been shown to be high in the Netherlands, ensuring complete medication histories of individuals [5]. Each record has information on the name of the drug, the date of dispensing, the amount dispensed, the dose regimen and the prescribing physician. The indication for each prescription is not registered. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO). The database does not include information on over-the counter medication and medication dispensed during hospitalization.

We selected from the IADB women aged 15 to 49 years with at least one prescription of AED (ATC code N03*) in 2006. AEDs were grouped into enzyme-inducing AEDs and non-enzyme-inducing AEDs as shown in Table 1. Lamotrigine has no significant effect on ethinylestradiol concentrations, but we labeled it as enzyme-inducing AED because it reduces the levonorgestrel level [7]. We also selected women from the IADB who had at least one prescription of a contraceptive (ATC G02B*, G03A*, G03HB01) in 2006. Selection of contraceptives was on the basis of HPK-codes (trade product codes) to distinguish different quantities of substances from contraceptives containing the same substances. Contraceptives were grouped into OCs containing estrogen 50 mcg, OCs containing estrogen lower than 50 mcg, IUDs and injectable contraceptives. We calculated the prevalence of contraceptives use and distribution of different contraceptive methods among enzyme-inducing AED users, non-enzyme-inducing AED users and women without AEDs. Analyses of differences in proportions were carried out using SPSS version 16.0. All p values were two-tailed and considered significant at $p<.05$.

This paper is approved by IADB.nl advisory board.

3. Results

From the IADB.nl database, we identified 1,630 women aged 15-49 years in the northern Netherlands who had received at least one prescription of AED in 2006. Of AED users, 888 (54.5%) used non-enzyme inducing AEDs and 742 (45.5%) used enzyme inducing AEDs. Of the AED using women 34.3% were prescribed highly effective contraceptives compared with 41.2% (57,682/140,012) for the general population of women aged 15-49 years ($p<.001$) (Table 2).

The distribution of different highly effective contraceptive methods among the AED-users and the general population is shown in Table 2. Women using AEDs and any highly effective contraceptive method more often received an OC with an estrogen content of 50 mcg compared to the general population (11.6% vs. 2.1%, $p<.001$). The significantly higher proportion of OC with an estrogen content of 50 mcg was even seen among women taking non-enzyme-inducing AEDs and using any highly effective contraceptive method (9.2% vs. 2.1%, $p<.001$). Of women who were prescribed any enzyme-inducing AED and any highly effective contraceptive method, 43.5% (97/223)

Table 2
Use of highly effective contraceptive methods among women in 2006, IADB.nl

	EI-AED (N=742)		Non-EI-AED (N=888)		p	General population[a] (N=140,012)		p1	p2
	N	%	N	%		N	%		
Prevalence of any highly effective contraception	223	30.1	336	37.8	.001	57682	41.2	<.001	.4
Distribution of contraceptive methods									
OC, contents =50 mcg estrogen	34	15.2	31	9.2	.2	1230	2.1	<.01	<.01
OC, contents <50 mcg estrogen	97	43.5	235	69.9	<.01	51371	89.1	<.01	<.01
Intrauterine device (IUD)	19	8.5	6	1.8	.01	2873	5	.2	.1
Injectable contraception	55	24.7	46	13.7	.04	1703	3	<.01	<.01
Combined[b]	18	8.1	18	5.4	.2	505	0.8	<.01	<.01

EI-AED: enzyme-inducing antiepileptic drug.
p1: compared with EI-AED users; p2: compared with non-EI-AED users.
[a] Exclude AED-users.
[b] Using more than one highly effective contraceptive method.

received a prescription of OC with an estrogen content less than 50 mcg. The corresponding values were significantly higher for non-enzyme-inducing AED users and for the general population. Compared to the general population, IUDs and injectable contraception were more frequently prescribed among women who received AEDs (22.5% vs. 7.9%, p<.001), in particular among enzyme-inducing AED users (33.2% vs. 7.9%, p<.001) (Table 2).

4. Discussion

We examined the prescription pattern of contraceptives co-prescribed with AEDs and showed that of women who used enzyme-inducing AEDs in combination with any highly effective contraceptive method, over 40% were on a low estrogen content OC. Epileptic women were more often on other contraceptive methods such as IUDs or injectable contraception compared with the general population.

Our results are similar to an early UK study, which showed that of epileptic women using both an enzyme-inducing AED and an OC, more than half took a low dose estrogen OC [4]. However, there was no information on use of IUDs or injectable contraception in that study. For women with epilepsy, planning their pregnancy is important given the teratogenic effects of some antiepileptic drugs. AEDs are increasingly being used in therapy for other conditions such as migraine, bipolar disorder, and pain. Thus, the teratogenic concerns do not only affect women with epilepsy. Contraception is an integral part of planning a pregnancy, but knowledge of the interactions between OCs and AEDs is unsatisfactory. An early survey in the US suggested that medical practitioners had limited knowledge of interactions between contraception and AEDs in women with epilepsy [8]. In another US study, only 4% of neurologists and none of the obstetricians knew the effects of the six most common AEDs on OCs [9]. A survey published in 2005 showed that about 70% of primary care physicians recognized that certain AEDs might interfere with the efficacy of OCs [10]. Moreover, women with epilepsy were poorly informed on the potential interaction between AEDs and OCs [11] and had limited knowledge of this issue [12]. In a cross-sectional questionnaire study among reproductive-age women with epilepsy presenting for routine outpatient visits to an urban, academic medical center, 50% of prior pregnancies were unplanned [13].

Women using AEDs were more frequently prescribed long-term contraceptive methods compared to general population, such as the IUDs which do not depend on hormonal changes for their contraceptive activity. These differences in prescribing patterns indicate that a number of physicians are aware that contraception in women on AED's should be optimally effective. Our study also indicated that women on non-enzyme-inducing AEDs were more frequently prescribed an OC with 50 mcg estrogen, which might not be necessary and predispose to increased thrombo-embolic risk. It is possible that prescribers were not aware which AEDs are enzyme inducers and which are not. In our study, highly effective contraceptive use among women using AEDs was lower than in the general population. It is consistent with a UK study which reported that 16.7% of the epileptic women were on an OC compared with 25% in the general population [4]. A limitation of our study is that there was no outcome data that could allow us to determine the differences of contraceptive failure between the women on enzyme-inducing AEDs and non-enzyme-inducing AEDs.

In summary, our study showed that many fertile age women using AEDs were not prescribed the correct dose of an oral contraceptive. Women who are on enzyme-inducing AEDs should not be prescribed low dose estrogen oral contraceptives. The hazard of contraceptive failure and unwanted pregnancy is greatly avoidable. Our results highlight the need for better education of prescribers regarding the interaction between AEDs and OCs, while pharmacists should play an active role.

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