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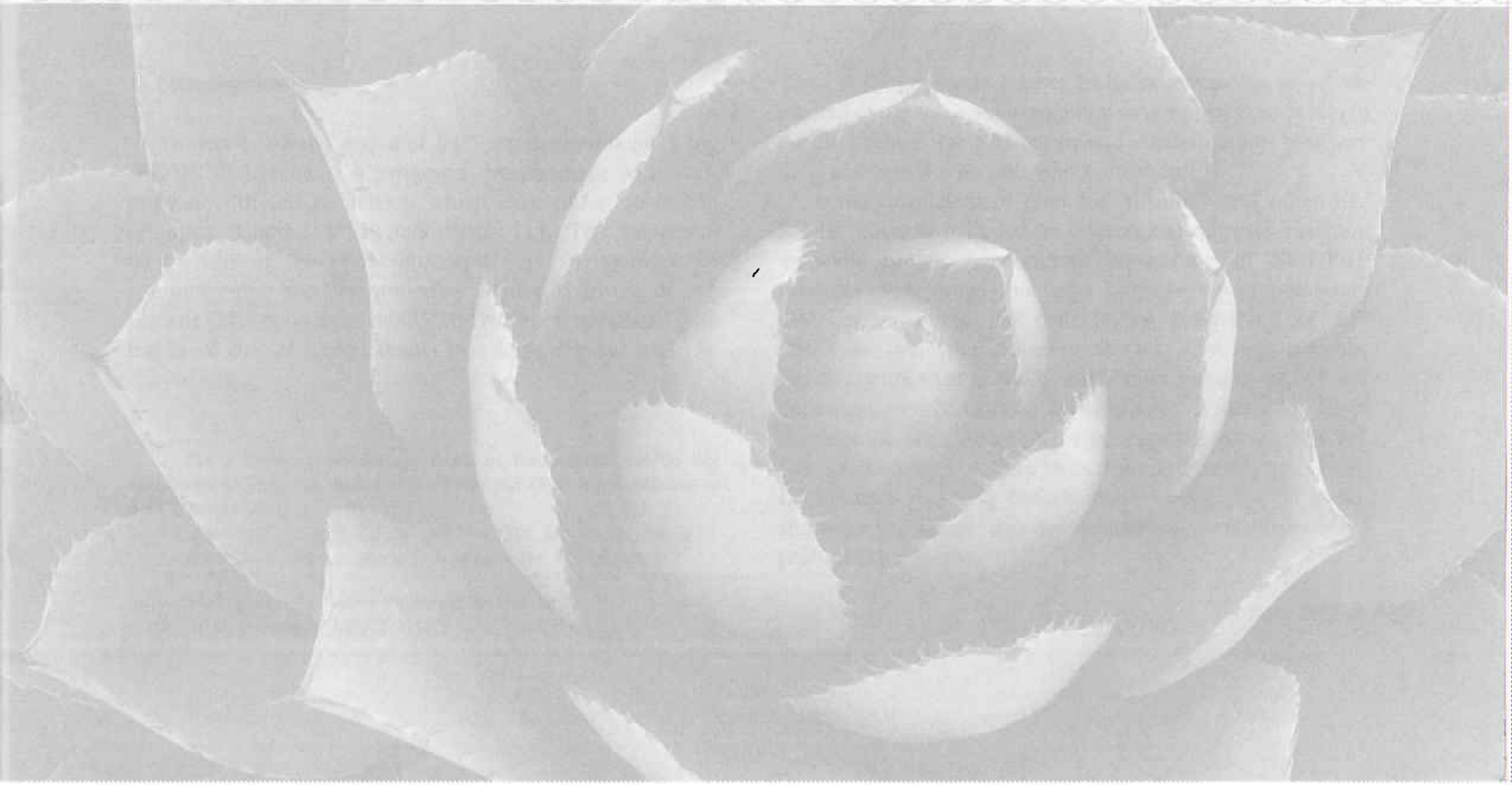

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Original research article

The concomitant prescribing of ethinyl estradiol/drospirenone and potentially interacting drugs☆

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Abstract

Background: Ethinyl estradiol 0.03 mg/drospirenone 3 mg (EE/DRSP) contains a progestin drospirenone with antimineralocorticoid properties that may cause potassium retention leading to hyperkalemia. We estimated the percentage of EE/DRSP users prescribed concomitant potassium-sparing drugs [nonsteroidal antiinflammatory drugs, diuretics, angiotensin-converting enzyme inhibitors (with diuretics), angiotensin II agonists (with diuretics), and potassium chloride] between January 1, 2002, and March 31, 2005.

Study Design: We analyzed a population-based data set of 62,527 EE/DRSP users (Dimension Rx™, Caremark). We compared the fill date and end date for each prescription (Rx) for an interacting drug to the start and end date for each EE/DRSP episode (linked Rxs). If a day of an interacting Rx overlapped with an EE/DRSP episode, concomitant prescribing was recorded.

Results: A total of 17.6% of the women concomitantly used EE/DRSP and an interacting drug. Twenty-nine percent of concomitant use occurred within a month of EE/DRSP initiation. Nonsteroidal antiinflammatory drugs and diuretics were most frequently used concomitantly with EE/DRSP. Forty percent of the women with concomitant use were 35 yearsof age or older at EE/DRSP initiation compared with 29% without concomitant use ($p<.001$). Obstetricians/gynecologists and family practitioners were the most common prescribers of EE/DRSP and potassium-sparing drugs, respectively.

Conclusions: Concomitant prescribing of EE/DRSP and potassium-sparing drugs occurred frequently in our study population. As EE/DRSP becomes more widely used, physicians prescribing it should monitor patients for potassium-sparing drug use.

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Keywords: Drospirenone; Concomitant treatment; Potassium sparing; Hyperkalemia; Progestin; Yasmin; Oral contraceptive

1. Introduction

Yasmin® [ethinyl estradiol 0.03 mg/drospirenone 3 mg (EE/DRSP)] contains a progestin drospirenone with antimineralocorticoid properties, which may cause potassium retention leading to hyperkalemia [1]. The progestin component of the oral contraceptive is an analogue of spironolactone and has properties similar to 25 mg of this diuretic [2]. Spironolactone (25 mg) has been associated with increased risk of hyperkalemia in a large clinical trial [3]. The EE/DRSP product label includes a warning to advise prescribers of the need to monitor serum potassium levels in the first month for patients treated concomitantly with any drug associated with potassium retention [4].

A risk management plan for Yasmin® and other EE/DRSP products included an educational outreach program to warn against concomitant prescribing of EE/DRSP products with drugs that may increase serum potassium [5]. Understanding the concomitant prescribing of EE/DRSP and drugs that induce potassium retention is of public health significance in the United States because use of oral contraceptives containing drospirenone is growing faster than use of other drugs in the oral contraceptive class [6]. Our study objectives were to estimate the percentage of EE/DRSP users receiving concomitant prescriptions for potassium-sparing drugs and to characterize population-based prescribing patterns.

☆ The opinions expressed are those of the authors and do not necessarily represent the views of the Food and Drug Administration or the US government.

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2. Materials and methods

We used population-based pharmacy dispensing records to identify women using EE/DRSP and to describe the concomitant prescribing of EE/DRSP with potassium-sparing drugs. The study cohort included women who were continuously eligible, between January 1, 2002, and March 31, 2005, for coverage by plans managed by a large pharmacy benefit manager, Caremark (Dimension Rx™). These data are anonymized, and subjects cannot be identified either directly or through identifiers. Therefore, this research was deemed exempt from the review of the institutional review board by the Food and Drug Administration's Research Involving Human Subjects Committee.

For each woman in the study cohort, we obtained information on prescriptions for potassium-sparing drugs during the study period. Potassium-sparing drugs included any drug from the following classes: nonsteroidal antiinflammatory drugs (NSAIDs), diuretics, angiotensin-converting enzyme (ACE) inhibitors, ACE inhibitors with diuretics, angiotensin II antagonists, angiotensin II antagonists with diuretics, or potassium chloride. We will refer to any drug from these classes as potassium sparing.

We examined the data for accuracy, removing claims in which the quantity or days supply was "unknown" or zero. For consistency, we removed patients with implausible EE/DRSP use from the data set and patients who aged more than 4 years over the 3-year study period. Overall, we removed 8.5% of claims (5.0% of patients). After limiting the population to women aged 10 years to 55 years old, we evaluated the concomitant prescribing of potassium-sparing drugs for 62,527 women taking EE/DRSP.

For each woman, we analyzed prescription claims data to evaluate whether she was concomitantly prescribed EE/DRSP and a potassium-sparing drug. We defined concomitant prescribing, a proxy for concomitant use, as the overlap of at least 1 day of a potassium-sparing drug prescription with any day during an EE/DRSP episode. An EE/DRSP episode was a continuous series of linked prescriptions in which no more than 30 days elapsed between the end of one prescription and the next prescription fill. We compared the fill date and end date for each potassium-sparing drug prescription to the start and end date for each EE/DRSP episode. We described the patient characteristics, such as age at EE/DRSP initiation, and patterns of concomitant prescribing, such as time until first concomitant use, concomitant use duration, and prescriber information. Descriptive statistics for continuous variables included mean and SD. To test for differences in means, we used a 2-sample t test, and for differences in proportions, we used a 2-proportion z test. We analyzed the data set using SAS version 8.2 (SAS Institute, Cary, NC).

3. Results

In our study, 17.6% of the women taking EE/DRSP had at least one concomitant prescription for a potassium-sparing drug during EE/DRSP therapy. Eighty-three percent of the women with concomitant therapy were not using a potassium-sparing drug at EE/DRSP initiation. For these women with concomitant prescribing occurring after the EE/DRSP initiation, the mean time to the first concomitant prescription was 161 days (range, 0–1171 days). Among these women, 28.9% filled their first prescription for a concomitantly used drug within the first month of EE/DRSP use and 62.9% within the first 6 months.

We found that 17.0% of women who had concomitant use were taking a potassium-sparing drug at EE/DRSP initiation. Our results suggest that women were prescribed a potassium-sparing drug that would eventually overlap with an EE/DRSP prescription up to 99 days before their EE/DRSP initiation. In addition, 64.4% of the women with concomitant prescribing in the first EE/DRSP episode, but not at EE/DRSP initiation, had a history of potassium-sparing drug use.

Ibuprofen was the most commonly used concomitant NSAID (26.9% of the concomitant NSAID claims). The diuretic drug class was dominated by spironolactone use. Though diuretics represent 18.2% of the concomitantly

Table 1
Characterization of concomitant use by drug class: the number of patients with concomitant use, the number of concomitantly used prescriptions, and the age at first EE/DRSP claim for women with concomitant prescriptions

	Overall	Non-NSAID	NSAID	ACE inhibitor	ACE inhibitor with diuretic	Angiotensin II agonist	Angiotensin II agonist with diuretic	Diuretic	Potassium chloride
No. of patients[a] (%)	11,019	2314 (21)	9320 (85)	460 (4)	114 (1)	278 (2.5)	225 (2)	1312 (12)	181 (2)
No. of prescriptions used concomitantly (% of all concomitant use)	29,934	11,953 (40.0)	17,981 (60.1)	2728 (9.1)	599 (2.0)	1560 (5.2)	1177 (3.9)	5441 (18.2)	448 (1.5)
Percentage of patients ≥35 years at first EE/DRSP prescription	40	58	36	72	70	77	72	48	65
Mean age (SD)	30.8 (10.2)	35.1 (9.8)	30.2 (10.1)	38.3 (7.9)	38.5 (6.9)	39.3 (7.7)	39.4 (7.7)	32.6 (10.2)	36.7 (9.1)

[a] More than one medication may be used concomitantly during the study. Percentages taken out of the total number of patients with concomitant use (11,019).

Table 2
Specialty of provider for EE/DRSP by the provider specialty for the concomitantly used medication

EE/DRSP provider specialty no. (%)	Concomitantly used drug provider specialty number (%)					
	Family practice	Internal medicine	OB/GYN	Unknown	Other	Total no. (%)
Family practice	1713 (5.7)	65 (0.2)	32 (0.1)	329 (1.1)	322 (1.1)	2461 (8.2)
Internal medicine	33 (0.1)	798 (2.7)	22 (0.1)	173 (0.6)	153 (0.5)	1179 (4.0)
OB/GYN	3047 (10.2)	2321 (7.8)	2856 (9.5)	3468 (11.6)	4644 (15.5)	16,336 (54.6)
Unknown	931 (3.1)	714 (2.4)	202 (0.7)	3232 (10.8)	1506 (5.0)	6585 (22.0)
Other	479 (1.6)	219 (0.7)	59 (0.2)	608 (2.0)	2008 (6.7)	3373 (11.2)
Total no. (%)	6203 (20.7)	4117 (13.8)	3171 (10.6)	7810 (26.1)	8633 (28.8)	29,934

prescribed potassium-sparing drugs (Table 1), spironolactone alone constituted 11.1%. We found that 11.0% of the concomitant drug prescribing lasted a week or less and 90.6% for a month or less. The mean duration of concomitant prescribing was 26.6 days (SD, 18.6). Nonsteroidal antiinflammatory drugs were the most commonly used concomitant drug class; the mean duration of concomitant NSAID use was longer than the duration of concomitant non-NSAID use (21.2 ± 15.1 days vs. 34.7 ± 20.4 days, $p<.001$). Women using non-NSAIDs concomitantly with EE/DRSP were, on average, older at the EE/DRSP initiation than those treated concomitantly with NSAIDs ($p<.001$) (Table 1).

Obstetricians/gynecologists (OB/GYNs) prescribed 54.6% of EE/DRSP prescriptions (Table 2). Of all concomitant events, 18.0% occurred when a potassium-sparing medication was prescribed by family practice or internal medicine specialists to a woman prescribed EE/DRSP by an OB/GYN. However, 9.5% of the concomitant prescribing was the result of an OB/GYN prescribing both medications (Table 2). OB/GYNs prescribed EE/DRSP concomitantly 1% when a dermatologist prescribed a potassium-sparing drug and 1.1% of the time when an endocrinologist prescribed a potassium-sparing drug. Table 2 shows that physicians of the same specialty (family practice, OB/GYN, or internal medicine specialists) prescribed 17.9% of all concomitantly used prescription pairs. Women filled both the EE/DRSP and the concomitant prescription on the same day for 22.1% of the concomitant prescription pairs. The same physician wrote 28.1% of the concomitantly prescribed potassium-sparing medications that were filled on the same day, and the physicians were most likely to be OB/GYNs specialists.

4. Discussion

Our results suggest that EE/DRSP was used concomitantly with drugs that may increase serum potassium. A previous study evaluated women using oral contraceptives to estimate the percentage of these women who received concomitant potassium-sparing drugs [7]. However, that study evaluated concomitant prescribing only at the EE/DRSP initiation. Therefore, their estimate of the percentage of EE/DRSP users with concomitant use was less than ours. Our concomitant prescribing definition included women using EE/DRSP who subsequently initiated a potassium-sparing drug. We did not limit our study to new EE/DRSP users who were taking a potassium-sparing drug at EE/DRSP initiation because we were interested in prescribing patterns that may lead to potassium retention.

Our data included a large insured population of EE/DRSP users, and we evaluated actual prescribing patterns. These women were a range of ages and from geographically diverse locations in the United States. We began collecting data 7 months after the United States approval of Yasmin®, the only approved EE/DRSP product during the study period. This study period helped ensure that, for many women, the first EE/DRSP claim was indeed their introduction to the product. Additionally, our definition of concomitance was broad, and we were able to record a wide range of use. Even a single day of overlap of a prescription for a potassium-sparing medication during an episode of Yasmin use was considered a concomitant drug use. However, a single day of overlap accounted for less than 1% of the concomitant prescribing.

We analyzed prescription claims data, which are subject to certain limitations. For example, we do not have information on prescription use but rather use prescribing as a proxy for use. Also, these data would not account for concomitant use of nonprescription NSAIDs. Oral contraceptives can be distributed as manufacturer samples [8]. Sampling will produce no prescription claims and not be recorded in the data set. Additionally, the data describing prescriber specialty were unknown for over 20% of the physicians in the data set. We could not identify concomitant prescribing in patients with medical conditions, which would put them at increased risk of hyperkalemia. This study was not able to examine whether potassium monitoring occurred, nor whether clinically important hyperkalemia occurred.

Our results suggests that current EE/DRSP prescribing patterns include concomitant prescribing either by physicians in the same specialty or in different specialties. A small survey of physicians who had previously prescribed EE/DRSP suggested that they generally agree with potassium testing for EE/DRSP users who have concomitant use with all potassium-sparing drugs except NSAIDs [7]. Our results

suggest that even physicians who do not specifically prescribe this oral contraceptive should nonetheless be aware that some commonly used potassium-sparing medications may interact with EE/DRSP. Prescribers should ask women about EE/DRSP use before initiating any potassium-sparing drugs, realizing that even months after the EE/DRSP initiation, the risk for hyperkalemia may remain. Physicians prescribing any drug-containing EE/DRSP may need to ask consistently over time about potassium-sparing drug use. This approach is important because our results suggest that the majority of patients who were concomitantly prescribed EE/DRSP were not taking a potassium-sparing drug at EE/DRSP initiation. Physicians should be aware of the potassium-sparing properties of drospirenone because use of oral contraceptives containing this progestin is growing faster than use of other oral contraceptives in the United States [6].

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NOTES

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