ELSEVIER

Contraception 75 (2007) 101–107

Contraception

Original research article

Serum potassium monitoring for users of ethinyl estradiol/drospirenone taking medications predisposing to hyperkalemia: physician compliance and survey of knowledge and attitudes☆

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Received 24 July 2006; revised 8 August 2006; accepted 26 August 2006

Abstract

Purpose: Yasmin-28 [ethinyl estradiol 0.03 mg/drospirenone 3 mg (EE/DRSP)] contains drospirenone, a progestin component that possesses antimineralocorticoid activity with a potassium-sparing diuretic effect similar to that in spironolactone. Product labeling recommends potassium monitoring in the first month of use for women concurrently receiving medication that may increase serum potassium.
Methods: We evaluated compliance with this recommendation by measuring monitoring around the date of oral contraceptive (OC) initiation in women who received EE/DRSP while being treated with medications predisposing to hyperkalemia and in similar women who received other OCs. Because preliminary analyses indicated incomplete compliance, we surveyed physicians who prescribed EE/DRSP to women receiving drugs predisposing to hyperkalemia on their knowledge and attitudes with regard to the recommendation. We conducted this study using data from the Ingenix Research Datamart, which includes insurance claims for reimbursement for medical services and prescription medications for approximately 8,000,000 members of a large nationally dispersed health plan. We used claims for pharmacy dispensings of prescription medications to identify all women aged 10–59 years old who initiated EE/DRSP or other OCs during the first 3 years of EE/DRSP availability (July 2001 to June 2004). The frequency of potassium monitoring was measured by identifying claims for serum potassium tests. We conducted a telephone survey of 58 physicians who had prescribed EE/DRSP up to June 2003 to women who received concomitant hyperkalemic drugs.
Results: Although potassium monitoring was generally more frequent among EE/DRSP initiators receiving concomitant hyperkalemic drugs than among other OC initiators receiving similar medications, only 40% of 466 EE/DRSP initiators with concurrent hyperkalemic treatment had potassium tests. More than 98% of surveyed physicians were aware of the potassium-sparing property of EE/DRSP. Compared with physicians whose patients had potassium tests, physicians of patients without such tests were more likely to disagree with the recommendation for users of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, heparin and nonsteroidal anti-inflammatory drugs. Patient barriers and health plan restrictions were other factors possibly contributing to noncompliance.
Conclusion: This study demonstrates incomplete physician compliance with a labeling recommendation of potassium monitoring for initiators of EE/DRSP receiving concomitant therapy predisposing to hyperkalemia. The limited compliance was likely due to a combination of selective physician acceptance of the recommendations and specific patient and health plan barriers to testing.

Keywords: Potassium monitoring; Oral contraceptives; Compliance; Physician survey

1. Introduction

The oral contraceptive (OC) Yasmin-28 [ethinyl estradiol 0.03 mg/drospirenone 3 mg (EE/DRSP)] contains the non-testosterone-derived progestin drospirenone, a component that possesses antimineralocorticoid activity with a potassium-sparing diuretic effect similar to that in spironolactone. When EE/DRSP first became available, a prominent clinical trial of spironolactone among persons with heart failure reported an increased risk of hyperkalemia in patients treated with spironolactone and angiotensin-converting enzyme (ACE) inhibitors, emphasizing the theoretical concern that drospirenone, a spironolactone analog, could similarly lead to hyperkalemia with clinical consequences [1]. Inadequate

☆ This study, which was conducted by i3 Drug Safety, was funded by a research contract from Berlex. The role of Berlex was limited to review of the manuscript. i3 Drug Safety retains final publication rights.

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doi:10.1016/j.contraception.2006.08.011

Table 1
Frequencies of initiators of EE/DRSP and other OCs receiving concurrent therapy with drugs that predispose to hyperkalemia, 7/1/01–6/30/04, Ingenix Research Datamart

Women with new dispensings	EE/DRSP (N=31,149) [n (%)]	Other OCs (N=360,505) [n (%)]
Women with new dispensings and concurrent therapy	466 (1.5)	7407 (2.1)
Concurrent therapy, by type[a]		
ACE inhibitors	173 (37.1)	3152 (42.6)
Angiotensin II inhibitors	70 (15.0)	1544 (20.8)
NSAIDs	90 (19.3)	1271 (17.2)
Potassium-sparing diuretics[b]	145 (31.1)	1769 (23.9)
Heparin	0 (0.0)	39 (0.5)

[a] Categories are not mutually exclusive because a woman could have more than one type of concurrent therapy.
[b] Including spironolactone.

electrolyte monitoring subsequently observed in older heart failure patients receiving spironolactone was hypothesized to increase the risk of hyperkalemia-related morbidity and mortality in patients treated with spironolactone [2]. To decrease the risk of hyperkalemia among EE/DRSP users, the product labeling for EE/DRSP recommends potassium monitoring in the first month of use for women concurrently receiving medication that may increase serum potassium [listed in the labeling as ACE inhibitors, angiotensin II inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, aldosterone antagonists and heparin]. EE/DRSP is contraindicated in women with conditions that might predispose to hyperkalemia (adrenal or renal insufficiency, or hepatic dysfunction).

As a condition of approval, the manufacturer conducted a postmarketing study of EE/DRSP to evaluate its use and association with hyperkalemic complications. As part of this larger effort, the current study was undertaken to assess compliance with EE/DRSP product labeling recommendations for potassium monitoring by physicians who prescribe EE/DRSP. We evaluated physician compliance with the labeling recommendation for potassium monitoring by measuring the frequency of potassium monitoring around the date of OC initiation in women who received EE/DRSP while being treated with medications predisposing to hyperkalemia. As a comparison, we also assessed potassium monitoring around the date of OC initiation in women who received other OCs while being treated with the same medications that might predispose to hyperkalemia. Because preliminary results on the frequency of potassium monitoring indicated that compliance was limited, we sought to elucidate underlying reasons for physician compliance with labeling recommendations. Accordingly, we surveyed physicians who prescribed EE/DRSP to women receiving concurrent hyperkalemic drugs on their knowledge and attitudes with regard to the potassium monitoring recommendation.

2. Materials and methods

We conducted this study using data from the Ingenix Research Datamart, which included insurance claims for reimbursement for medical services and prescription medications for approximately 8,000,000 members of a large nationally dispersed health plan. We used claims for pharmacy dispensings of prescription medications to identify all women aged 10–59 years old who initiated EE/DRSP during the first 3 years of EE/DRSP availability (July 2001 to June 2004). A woman was eligible for inclusion if she was enrolled as a health plan member for 3 months prior to the date of initial OC dispensing and 2 months subsequent to this date. An initial EE/DRSP dispensing was defined as a first dispensing to a woman enrolled for 90 days prior to the dispensing without a previous EE/DRSP dispensing in the same period. We similarly defined the initiation of other OCs as the occurrence of a first dispensing of a non-EE/DRSP OC to a woman enrolled for 90 days prior to the dispensing without a dispensing of the same OC brand. If a woman was dispensed more than one brand of OC in a quarter, only the first dispensing was counted.

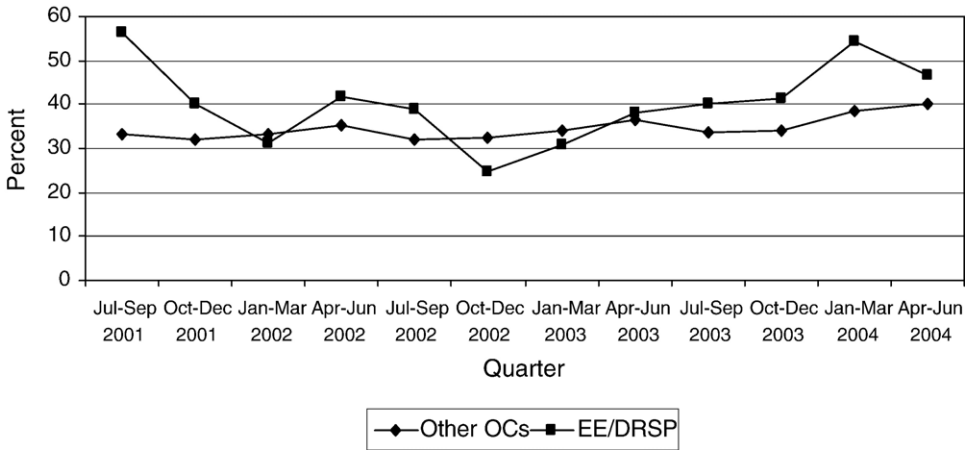

Fig. 1. Potassium monitoring among EE/DRSP and other OC initiators receiving concurrent therapy with drugs that predispose to hyperkalemia, by calendar quarter (7/1/01–6/30/04), Ingenix Research Datamart.

Table 2
Frequency of potassium monitoring among initiators of EE/DRSP and other OCs receiving concurrent therapy with drugs that predispose to hyperkalemia, by month, in relation to OC initiation[a], 7/1/01–6/30/04, Ingenix Research Datamart

Women with new dispensings and concurrent therapy	EE/DRSP (N=466) [n (%)]	Other OCs (N=7407) [n (%)]
Potassium monitoring		
2 months after initiation	36 (7.7)	561 (7.6)
Month after initiation	36 (7.7)	540 (7.3)
Day of initiation	7 (1.5)	71 (1.0)
Month before initiation	61 (13.1)	754 (10.2)
2 months before initiation	36 (7.7)	613 (8.3)
3 months before initiation	49 (10.5)	651 (8.8)
Any (of the above)	186 (39.9)	2568 (34.7)

[a] Categories are not mutually exclusive because a woman could have more than one claim for potassium monitoring.

Due to the availability of professional samples, the actual date of OC initiation may have been earlier than the date of first pharmacy dispensing. Conversely, the actual date of OC initiation may have occurred after the date of first pharmacy dispensing. Accordingly, we measured the frequency of potassium monitoring by identifying claims for serum potassium tests during the 3 months before and the 2 months after initial dispensing. We tabulated the frequency of potassium testing in EE/DRSP or other OC initiators receiving concomitant therapy with drugs predisposing to hyperkalemia for each calendar quarter between July 2001 and June 2004. The identification of serum tests using claims has been recently validated with medical record data [3].

Using information on dispensing dates and days supplied, we defined exposure to drugs predisposing to hyperkalemia as listed in the EE/DRSP labeling (ACE inhibitors, angiotensin II inhibitors, NSAIDs, potassium-sparing diuretics, aldosterone antagonists and heparin). Current exposure was defined as beginning with the date of dispensing and extending through the end of days supplied plus 7 days in relation to each dispensing. Dispensing of EE/DRSP or other OCs during a period of current exposure was considered concomitant therapy. For NSAIDs, the EE/DRSP label specifies that concomitant use be characterized by both concurrent use and chronic use; thus, we required that a woman both be a current user (as defined above) and have at least 60 days supplied by dispensings in the 90 days preceding the initial EE/DRSP or other OC dispensings.

Because preliminary analyses suggested incomplete compliance with the potassium monitoring recommendation, we sought to elucidate physicians' attitudes and knowledge regarding the recommendation. Accordingly, we developed a telephone survey with specific items on: awareness of EE/DRSP properties and prescribing guidelines, attitudes toward recommendations for monitoring, and timing and patient barriers to monitoring. In January 2004, we administered the survey to physicians who had prescribed EE/DRSP to initiators who received concurrent medication predisposing to hyperkalemia and were identified from July 2001 to June 2003, the latest date for which complete dispensing data were available at the time of survey. First, we identified all eligible EE/DRSP initiators who met labeling criteria for recommended monitoring (n=296). We then identified the physicians who prescribed EE/DRSP to these women and compiled a list of 219 physicians to survey.

The survey consisted of a telephone interview that followed a mailed introductory letter. The letter invited the physicians to take part in a telephone survey designed to elucidate physicians' knowledge and opinion of labeling recommendations. The letter offered the physicians the option of calling a toll-free number to participate or of waiting for a call from a trained interviewer. Fifty-eight physicians who had each prescribed EE/DRSP to at least one patient receiving concomitant medication predisposing to hyperkalemia participated in the survey.

Physician survey responses were linked to claims for potassium monitoring in the Ingenix Research Datamart. We tabulated responses to survey items overall and according to the presence of claims for potassium monitoring. We used SAS version 8.2 to generate percentages for all descriptive analyses.

This study, including the invitation letter and the survey instrument, received appropriate Institutional Review Board approval by the New England Institutional Review Board.

3. Results

Table 1 shows the proportion of EE/DRSP and other OC initiators who received concomitant medications predisposing to hyperkalemia for the first 3 years after EE/DRSP launch. In general, OCs were infrequently prescribed to users of drugs predisposing to hyperkalemia. Compared to other OCs, EE/DRSP was prescribed 28% less often to women with concomitant use of drugs predisposing to hyperkalemia; 1.5% of EE/DRSP initiators (n=466) and 2.1% of other OC initiators (n=7407) had claims indicating concurrent use

Table 3
Potassium monitoring physician survey response, by specialty and by region of practice[a]

	Contacted (N=219) [n (%)]	Participated (N=58) [n (%)]
Specialty		
Obstetrics/gynecology	178 (81.3)	48 (82.8)
Family practice/general practice	29 (13.2)	7 (12.1)
Internal medicine/general internal medicine	7 (3.2)	2 (3.4)
Endocrinology	2 (0.9)	1 (1.7)
Allergy	1 (0.5)	0 (0.0)
Emergency medicine	1 (0.5)	0 (0.0)
General surgery	1 (0.5)	0 (0.0)
Region of practice		
Northeast	7 (3.2)	2 (3.4)
South	108 (49.3)	35 (60.3)
Central	88 (40.2)	17 (29.3)
West	16 (7.3)	4 (6.9)

[a] Determined from claims records.

Table 4
Potassium monitoring physician survey results, overall and by presence of claims for potassium test

Survey item	All participants ($N=58$) [n (%)]	Potassium test[a] ($n=27$) [n (%)]	No potassium test ($n=31$) [n (%)]
Patients prescribed EE/DRSP in the past year			
<25	9 (15.5)	5 (18.5)	4 (12.9)
25–99	19 (32.8)	6 (22.2)	13 (41.9)
≥100	30 (51.7)	16 (59.3)	14 (45.2)
Aware of the unique properties of drospirenone			
Yes	56 (96.6)	25 (92.6)	31 (100.0)
No	2 (3.4)	2 (7.4)	0 (0.0)
Aware that prescribing guidelines differ from those of other OCs			
Yes	47 (81.0)	22 (81.5)	25 (80.6)
No	11 (19.0)	5 (18.5)	6 (19.4)
Aware that drospirenone has potassium-sparing diuretic effect			
Yes	57 (98.3)	27 (100.0)	30 (96.8)
No	1 (1.7)	0 (0.0)	1 (3.2)
Met with a representative of the EE/DRSP manufacturer between 2001 and the time of survey			
Yes	54 (93.1)	25 (92.6)	29 (93.5)
No	4 (6.9)	2 (7.4)	2 (6.5)
Discussed contraindications to prescribing EE/DRSP with representative[b]			
Yes	34 (63.0)	15 (60.0)	19 (65.5)
No	20 (37.0)	10 (40.0)	10 (34.5)
Discussed recommendations for potassium testing with representative[b]			
Yes	19 (35.2)	9 (36.0)	10 (34.5)
No	35 (64.8)	16 (64.0)	19 (65.5)
Agreed with testing for users of ACE inhibitors, angiotensin II receptor antagonists or heparin			
Yes	45 (77.6)	24 (88.9)	21 (67.7)
No	12 (20.7)	3 (11.1)	9 (29.0)
Preferred not to answer/unknown	1 (1.7)	0 (0.0)	1 (3.2)
Agreed with testing for users of potassium-sparing diuretics or aldosterone antagonists			
Yes	55 (94.8)	25 (92.6)	30 (96.8)
No	3 (5.2)	2 (7.4)	1 (3.2)
Agreed with testing for NSAID users			
Yes	13 (22.4)	6 (22.2)	7 (22.6)
No	43 (74.1)	19 (70.4)	24 (77.4)
Preferred not to answer/unknown	2 (3.4)	2 (7.4)	0 (0.0)
Optimal time to test serum potassium			
Before initial dispensing visit	5 (8.6)	1 (3.7)	4 (12.9)
At the time of first dispensing or visit	9 (15.5)	5 (18.5)	4 (12.9)
During the first contraceptive treatment cycle	10 (17.2)	5 (18.5)	5 (16.1)
After the first contraceptive cycle	22 (37.9)	10 (37.0)	12 (38.7)
At the next visit	2 (3.4)	1 (3.7)	1 (3.2)
Within the first 6 months	9 (15.5)	4 (14.8)	5 (16.1)
Other/unknown	1 (1.7)	1 (3.7)	0 (0.0)
Percent of patients for whom test was ordered who were tested			
100	16 (27.6)	7 (25.9)	9 (29.0)
76–99	24 (41.4)	10 (37.0)	14 (45.2)
51–75	5 (8.6)	5 (18.5)	0 (0.0)
26–50	4 (6.9)	1 (3.7)	3 (9.7)
≤25	9 (15.5)	4 (14.8)	5 (16.1)
If another physician was testing the patient for other reasons (e.g., routine care), participant would			
Follow recommendation anyway	9 (15.5)	3 (11.1)	6 (19.4)
Not be likely to order test	3 (5.2)	3 (11.1)	0 (0.0)
Call the other physician to obtain test results	36 (62.1)	17 (63.0)	19 (61.3)
Ask the patient for test results	8 (13.8)	3 (11.1)	5 (16.1)
Would not know if patient was seen by another physician	1 (1.7)	1 (3.7)	0 (0.0)
Other/unknown	1 (1.7)	0 (0.0)	1 (3.2)
Physician-identified patient and health plan barriers to potassium testing			
Cost to patient	18 (31.0)	9 (33.3)	9 (29.0)
Patient time constraints/availability	27 (46.6)	13 (48.1)	14 (45.2)
Patient aversion to blood test	25 (43.1)	10 (37.0)	15 (48.4)
Health plan limitations on test ordered	22 (37.9)	9 (33.3)	13 (41.9)
Other/unknown	22 (37.9)	14 (51.9)	8 (25.8)

[a] Patient had at least one claim for serum potassium test.
[b] Restricted to 54 respondents who stated that they met with a manufacturer representative between 2001 and the date of the survey.

(Table 1). The most frequently occurring drug class predisposing to hyperkalemia was ACE inhibitors.

Fig. 1 presents the percentage of initiators of EE/DRSP or other OCs with concurrent therapy predisposing to hyperkalemia who had claims for baseline potassium monitoring tests by calendar quarter during the first 3 years of EE/DRSP availability. For EE/DRSP initiators receiving drugs predisposing to hyperkalemia, the frequency of potassium monitoring ranged from 24.5% to 56.3%. Potassium monitoring was generally more frequent among EE/DRSP initiators receiving concomitant hyperkalemic drugs than among other OC initiators receiving similar medications. Overall, 39.9% of EE/DRSP initiators and 34.7% of other OC initiators had claims evidence of baseline potassium monitoring during the first 3 years of product availability (Table 2). Thus, EE/DRSP initiators were 15% more likely to have potassium monitoring. Claims for potassium monitoring were most common in the month before the initiation for both EE/DRSP initiators (13.1%) and other OC initiators (10.2%). Approximately 8% of EE/DRSP initiators had potassium monitoring in the first month after initiation.

Of 219 physicians contacted for the potassium monitoring survey, 58 (26%) responded. Table 3 shows the distributions by specialty and by region of participating physicians and the larger pool of contacted physicians. Approximately 83% of the participants were obstetrician/gynecologists. More than 60% of participants practiced in the southern region of the United States.

Table 4 presents the frequencies of physician responses to survey questions, overall and according to whether the patient(s) had claims evidence of baseline potassium monitoring. Compared to physicians of patients lacking potassium tests, physicians of patients with monitoring claims were more likely to have written a higher volume of EE/DRSP prescriptions in the year before the survey.

Overall, 98.3% of participants were aware that DRSP has a potassium-sparing diuretic effect, and 81.0% were aware that prescribing guidelines for EE/DRSP differed from those of other OCs. Ninety-three percent of all participants reported having met with a manufacturer representative. Less than two thirds of providers recalled discussing contraindications to prescribing EE/DRSP with the representative, and approximately one third reported discussing monitoring guidelines. We did not observe any substantial differences in awareness or in the content of representative discussions according to whether the physician's patient had claims for monitoring.

Compared to physicians whose patients had potassium tests, physicians whose patients lacked tests were more likely to disagree with the monitoring recommendation for users of ACE inhibitors, angiotensin II receptor antagonists and heparin (29.0% vs. 11.1%). Over 90% of all surveyed physicians agreed with the recommendation for users of potassium-sparing diuretics or aldosterone antagonists. However, more than 70% of all physicians disagreed with the recommendation for NSAID users; a higher proportion of physicians of patients without tests disagreed (70.4% and 77.4% for the presence and the absence of potassium monitoring, respectively).

The participating physicians most often indicated that the optimal time to test was after the first contraceptive cycle; only 17.2% indicated that the optimal testing period was during the first cycle of use. Overall, the majority of participants estimated that more than 75% of patients for whom tests were ordered were actually tested. Physicians whose patients lacked monitoring claims were more likely to estimate that 50% or fewer of such patients were actually tested. If another physician was already testing the patient for other reasons, most participants indicated that they would contact the other provider for test results; only 16% indicated that they would follow the monitoring recommendation even if another physician was already monitoring the patient. Physicians identified health plan limitations on potassium testing, patient aversion to blood tests and patient time constraints as possible factors contributing to noncompliance. Patient aversion to blood tests and health plan restrictions were identified more often by physicians whose patients lacked evidence of testing.

4. Discussion

Although baseline potassium monitoring was more frequent among women initiating EE/DRSP who also received concurrent therapy with drugs that predispose to hyperkalemia than among similar women initiating other OCs, 60% of EE/DRSP initiators dispensed hyperkalemic medications did not have baseline potassium tests. We observed that EE/DRSP was less likely to be dispensed than other OCs to users of drugs predisposing to hyperkalemia, which suggests that some physicians may have avoided prescribing EE/DRSP to such patients altogether rather than follow monitoring guidelines.

The survey results indicate that the prescribing physicians were generally aware of EE/DRSP's potassium-sparing effects and prescribing guidelines. Only a third of providers recalled discussing monitoring recommendations with a manufacturer representative, suggesting that increasing this fraction might improve compliance. However, we did not observe any substantial differences, according to the presence of monitoring, in awareness or in reported discussions of monitoring. Unpublished data from the manufacturer suggest that physicians may not have distinguished between representatives of the EE/DRSP manufacturer and representatives of other manufacturers. Thus, the percentages of participants who recalled discussing recommendations or contraindications may be inaccurately low.

Physician disagreement with the need for potassium monitoring with regard to the use of ACE inhibitors, angiotensin II receptor antagonists and heparin, which together account for over 50% of concurrently used drugs predisposing to hyperkalemia and, to a lesser degree, with

regard to NSAID use, may be responsible for a substantial portion of noncompliance with monitoring recommendations. In some cases, physicians may have ordered tests, but possible barriers, such as patient aversion to blood tests, health plan limitations and patient time constraints, may have led to noncompliance. The study population of OC users was generally young and healthy, which may have led to further noncompliance, since compliance with laboratory monitoring recommendations tends to increase with age and with the prevalence of comorbidities. Other factors underlying noncompliance have been identified in the literature, including clinical perceptions of low risk, inaccessible records of medication use, lack of tracking and reminder tools, and time constraints [4].

Previous studies have reported incomplete compliance with labeling recommendations and published guidelines for laboratory monitoring [3–6]. A recent cross-sectional study of 10 large health maintenance organizations found that the frequency of baseline electrolyte monitoring ranged from 20% to 62%, depending on the drug [3]. The frequency of baseline potassium monitoring observed for EE/DRSP falls well within this range. Even with strong regulatory actions such as black box warnings and the Food and Drug Administration's most stringent labeling recommendations for drugs carrying risks of serious injury or death, compliance is often inadequate [7–9].

The underlying motivation for undertaking this study of potassium monitoring was the hypothesis that drospirenone, a spironolactone analog, might confer an increased risk of hyperkalemia, especially among women with predisposing characteristics. However, recent studies of drospirenone have not detected an increased risk of hyperkalemia among users and suggest that, generally, it is safe and well tolerated in the populations of users studied [10,11]. In a study expressly designed to examine the risk of hyperkalemia associated with drospirenone in a high-risk population, Preston et al. [10] found no difference in the rate of hyperkalemia among hypertensive postmenopausal women aged 44–70 years, with and without type 2 diabetes, who were treated with 3 mg of drospirenone (the equivalent of a 25-mg dose of spironolactone) while receiving ACE inhibitors or angiotensin receptor antagonists, and similar women receiving placebo. Notwithstanding incomplete compliance with potassium monitoring recommendations, we did not observe an increase in hyperkalemic events in our study population of relatively healthy young OC users [11] associated with EE/DRSP, which has a drospirenone dose equivalent to 25 mg of spironolactone and thus smaller than the therapeutic dose of spironolactone used for hirsutism (100–200 mg/day).

The strengths of this study include the ability to evaluate compliance with potassium monitoring recommendations using claims data that captured all reimbursed medical services. We were able to selectively target for survey providers who prescribed EE/DRSP to patients receiving concurrent medication predisposing to hyperkalemia. Furthermore, we linked survey results on physician attitudes and knowledge with claims evidence for potassium monitoring. Thus, we were able to evaluate the effectiveness of medical education efforts with regard to EE/DRSP. To the best of the authors' knowledge, this is the first report on the frequency of potassium monitoring in a population of healthy young OC users and of a survey of physicians' knowledge and attitudes regarding potassium monitoring recommendations by a manufacturer. Because this study was conducted in a large nationally diverse health plan, results may be generalized to similar OC users in the United States.

Notwithstanding low survey participation, we observed similarities between participating providers and the larger pool of eligible providers in terms of medical specialty and region of practice, which did not indicate that respondents differed from nonrespondents. The survey, which was conducted among physicians who prescribed OCs up to June 2003, captures physician awareness and attitudes during the first 2 years of EE/DRSP availability, prior to recent reports suggesting no association between EE/DRSP and hyperkalemia [10,11]. The survey responses were subject to self-report bias that could have led to an overestimate of the degree of awareness or agreement with recommendations among participants. However, because the survey was voluntary and confidential, this bias may be minimal.

Other caveats to these findings are related to the limitations of claims data. It was not possible to determine whether the prescribing physician surveyed was the provider who ordered the potassium tests or whether physicians were aware of test results. However, the survey responses suggest that the prescribing physicians of patients with potassium monitoring claims were more likely than those of patients without such claims to order potassium tests. Because it was not possible to determine when a patient failed to take a test that her provider had ordered, we were not able to assess patient compliance and physician compliance separately. We also could not describe underlying clinical decisions or motivations regarding monitoring. Dispensings or tests would not have been captured in this claims-based study if payments were not administered through the health plan. Due to the widespread use of samples, the date of actual OC initiation may have been earlier than the date of first pharmacy dispensing, which was used as our operational definition for OC initiation. Accordingly, the distribution of the time period of monitoring may be inaccurately skewed to months before initiation (as defined by first dispensing).

In conclusion, this study demonstrates incomplete physician compliance with a manufacturer labeling recommendation of potassium monitoring for initiators of EE/DRSP receiving concomitant therapy predisposing to hyperkalemia. The limited compliance was likely due to a combination of selective physician acceptance of the recommendations and specific patient and health plan

barriers to testing. This study provides useful information for similar laboratory monitoring efforts among OC users and related medical education campaigns.

Acknowledgments

We are indebted to Lisa Weatherby, Hassen Abdulkerim, Najat Ziyadeh and Robin Clifford for analytic support and to the members of the Yasmin Scientific Advisory Board (Edward L.C. Pritchett, M.D., Bertram Pitt, M.D., Mary Lake Polan, M.D., and Christopher S. Wilcox, M.D., Ph.D.).

References

[1] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.

[2] Shah KB, Krishnamurti R, Sawyer R, Gottleib SS. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. J Am Coll Cardiol 2005;46:845–9.

[3] Raebel MA, Lyons EA, Andrade SE, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120–6.

[4] Hurley JS, Roberts M, Solberg LI, et al. Brief report: laboratory safety monitoring of chronic medications in ambulatory care settings. J Gen Intern Med 2005;20:331–3.

[5] Raebel MA, McClure DL, Simon SR, et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Pharmacoepidemiol Drug Safety [Published online Feb 8, 2006].

[6] Walker AM, Bortnichak EA, Lanza L, Yood RA. The infrequency of liver function testing in patients using nonsteroidal anti-inflammatory drugs. Arch Fam Med 1995;4:24–9.

[7] Wagner AK, Chan KA, Dashevsky I, et al. FDA drug prescribing warnings: is the black box half empty of half full? Pharmacoepidemiol Drug Safety 2006;15:369–86.

[8] Graham DJ, Drinkard CR, Shatin D, Tsong YI, Burgess MJ. Liver enzyme monitoring in patients treated with troglitazone. JAMA 2001; 286:831–3.

[9] Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: temporal trends in relation to the sending of 'Dear Doctor' letters. Pharmacoepidemiol Drug Saf 2001;10:211–8.

[10] Preston RA, William WB, Pitt B, Bakris G, Norris PM, Hanes V. Effects of drospirenone/17-β estradiol on blood pressure and potassium balance in hypertensive postmenopausal women. Am J Hypertens 2005;18:797–804.

[11] Loughlin J, Seeger JD, Eng PM, Clifford RC, Cutone J, Walker AM. Risk of hyperkalemia in women taking ethinyl estradiol/drospirenone and other oral contraceptives [submitted for publication].