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Original Research

Retrospective analysis of adverse events with spironolactone in females reported to the United States Food and Drug Administration

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ABSTRACT

Background: Spironolactone is an off-label acne treatment that is commonly prescribed due to its low cost, efficacy, and tolerability.
Objective: This study aimed to classify the most common adverse reactions associated with spironolactone in women of all ages and analyze the relative risk of hyperkalemia for different age groups.
Methods: The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database was analyzed for common adverse reactions associated with female patients taking spironolactone. Reported hyperkalemia adverse events with spironolactone were further subdivided by age group. Google Trends was used to examine public interest, and Altmetric was used to quantitate scholarly mentions of spironolactone. Yearly data were compared with adverse events in the FAERS database.
Results: The most common adverse reaction in women taking spironolactone was hyperkalemia (16.1% of all adverse events), but it was extremely uncommon in women age ≤45 years (1.9% of all hyperkalemia cases). Increased Google searches and scholarly mentions in the Altmetric database for spironolactone were also associated with increased reporting of adverse events in the FAERS database for men and women combined.
Conclusion: Women taking spironolactone should be counseled that hyperkalemia is the most common adverse event but is uncommon in those age ≤45 years. Public and academic interest in spironolactone has increased in recent years, and although prescribing data are not available, this interest may account for the increased reporting to FAERS during the same time period.

Introduction

Spironolactone, a synthetic 17-lactone, has antagonistic effects on progesterone and androgen receptors and has been used as an off-label treatment for acne in women (Barbieri et al., 2019; Charny et al., 2017; Muhlemann et al., 1986). Numerous guidelines have recommended its off-label use for acne therapy to avoid antibiotic resistance and potential side effects (Fleming-Dutra et al., 2016; Goodfellow et al., 1984; Levy et al., 2003; Nast et al., 2012; Stewart et al., 2006; Zaenglein and Thiboutot, 2006; Zaenglein et al., 2016). Spironolactone's mechanism of action is through inhibition of sebocyte androgen receptors, thereby reducing sebum production. Acne dosing is 25 to 200 mg/day.

The medication is generally well tolerated, with the most common adverse event being irregular menstruation (15%-30%), which is dose dependent and mitigated by oral contraceptives or an intrauterine device (Hughes and Cunliffe, 1988; Layton et al., 2017). Other less common side effects are urinary frequency, dizziness, headaches, nausea, vomiting, breast tenderness, and breast enlargement (Layton et al., 2017; Shaw and White, 2002). Because spironolactone is a potassium sparing diuretic, hyperkalemia is another potential adverse effect that has been reported in patients with renal insufficiency or congestive heart failure, particularly at high doses (Juurlink et al., 2004; U.S. Food and Drug Administration [FDA], 2008). Potassium levels are often routinely monitored for patients taking spironolactone for the FDA-approved indications hypertension and heart failure according to recommendations in the prescribing information (FDA, 2008a, 2008b).

Controversy exists regarding whether serum potassium monitoring is necessary or beneficial when spironolactone is used to treat acne in an otherwise healthy woman. Laboratory monitoring may be a deterrent for patients and increases the cost of an otherwise inexpensive and well-tolerated acne medication. In this study, our goals were to classify adverse events and evaluate the inci-

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dence of reporting of hyperkalemia among women taking spironolactone, using the FDA Adverse Event System Reporting Database (FAERS; FDA, 2019).

Methods

Study design

A retrospective analysis of adverse events with spironolactone between January 1, 1969 to December 30, 2018 was performed using the FAERS database (FDA, 2019). This database includes all adverse events associated with a medication as reported to the FDA by patients, health care providers, and pharmaceutical companies. Male patients were excluded from the FAERS hyperkalemia analysis. The number of adverse events in the FAERS database was further subdivided into the number of cases reported annually and by age group as predefined in FAERS (2 months to 2 years, 3–11 years, 12–17 years, 18–45 years, 46–64 years, 65–85 years, and unspecified age). The FAERS database did not allow for an analysis of spironolactone adverse events by specific indication (acne), so all indications were included. The database also did not allow controlling for comorbidities and concomitant medications.

Google Trends measures interest in a particular topic through Google searches (Google, 2019). Altmetric is a database that tracks online interest/mentions and scholarly publications on a specific topic by aggregating data from multiple media and online sources (Altmetric, 2019). We used Google Trends (Google, 2019) and Altmetric (Altmetric, 2019) to analyze yearly public interest and scholarly publications on/interest in spironolactone during overlapping time periods with the yearly FAERS data on spironolactone. The yearly search trend for the term "spironolactone" between 2004 and 2018 (United States) was downloaded from Google in September 2019, and yearly search results for the term "spironolactone" were compared with the number of adverse events reported to the FAERS per year for spironolactone. FAERS adverse events with spironolactone for both men and women were used for this comparison because Google Trends data can not be subdivided by sex. Online mentions for the term "spironolactone" by year were downloaded from the Altmetric database from 1987 to 2018 and compared with the number of adverse events from spironolactone reported to the FAERS database per year. Our Altmetric search included worldwide data, but the search excluded non-English publications. Eighty-five percent of publications originated from the United States.

Statistical analyses

Spearman's rank correlation coefficient was used to analyze possible associations between the number of adverse events reported to FAERS and the yearly Google Trends search results and yearly Altmetric mentions.

Results

During the study period, 7920 adverse events with spironolactone were reported to FAERS for women of all ages. The top 20 most commonly reported adverse events are listed in Table 1. Hyperkalemia (n = 1272; 16.06%), kidney injury (n = 1204; 15.2%), and drug interactions (n = 710; 8.96%) were most often reported. Adverse events such as polyuria (n = 22; 0.28%), menstrual disorder (n = 21; 0.27%), and breast swelling (n = 9; 0.11%) were less frequently reported.

In the FAERS database, hyperkalemia cases reported in women were not evenly distributed across age groups. There were a total of 1272 cases: 2 months to 2 years (2, 0.16%), 3 years to 11 years (9, 0.7%), 12 years to 17 years (1, 0.08%), 18 years to 45 years (13, 1%), 46 years to 64 years (171, 13.44%), 65 years to 85 years (754, 59.28%), and "not specified" (27, 2.12%) (Fig. 1).

Table 1
Top 20 most commonly reported adverse events reported with spironolactone in the U.S. Food and Drug Administration Adverse Event Reporting System database from January 1, 1969 to December 30, 2018.

Category	n	%
Hyperkalemia	1272	16.06
Acute kidney injury	1204	15.20
Drug interaction	710	8.96
Hyponatremia	665	8.40
Dehydration	483	6.10
Hypotension	398	5.03
Fall	377	4.76
Nausea	356	4.49
Diarrhea	346	4.37
Dyspnea	335	4.23
Bradycardia	321	4.05
Dizziness	321	4.05
Renal Failure	317	4.00
Blood creatinine increased	311	3.93
Malaise	302	3.81
Asthenia	298	3.76
Vomiting	288	3.64
Drug ineffective	261	3.30
Confusional state	258	3.26
Fatigue	220	2.78

Although overall spironolactone prescribing data were not available, we sought to compare yearly adverse events in the FAERS database with annual public interest in spironolactone using the Google Trends search term "spironolactone" and annual scholarly mentions of spironolactone in the Altmetric database. During the overlapping time periods, there was an increase in both the number of cases reported to FAERS and the Google Trends search, with an isolated dip in 2016. During the overlapping periods, there was an increase in both the FAERS and Altmetric curves, with a sharp increase for Altmetric in 2015 and then an isolated dip in 2016 for both FAERS and Almetric (Fig. 2). There was a strong correlation between the number of cases reported to the FDA and the Google Trends search (Spearman-rank coefficient testing: $R = .94$; $p < .001$). There was also a strong correlation between the number of cases reported to the FDA and the Altmetric mentions (Spearman-rank coefficient testing: $R = .64$; $p < .01$).

Discussion

During the study period, hyperkalemia was the most commonly reported side effect in women taking spironolactone, accounting for 16.06% of all adverse reactions. However, the majority of these cases occurred in older age groups and was exceptionally rare in women aged ≤45 years (1.9%). Women aged 46 to 64 years were 13 times more likely to suffer from hyperkalemia than women aged 18 to 45 years. Women ≥65 years old were most at risk for hyperkalemia, being 58 times more likely to have hyperkalemia than women aged 18 to 45 years and 4.4 times more likely than women aged 46 to 64 years.

Our data support and add to the previous literature. For example, Plovanich et al. (2015) analyzed 1802 serum potassium measurements from healthy female patients with acne, aged 18 to 45 years (mean: 27.5 years), and only 13 patients (0.72%) had elevated potassium levels. Because none of the patients were older than 45, the authors could not draw any conclusions for older women. In a retrospective study by Thiede et al. (2019), the authors measured potassium levels in 124 healthy women taking spironolactone for acne. Elevated potassium levels were seen in 1

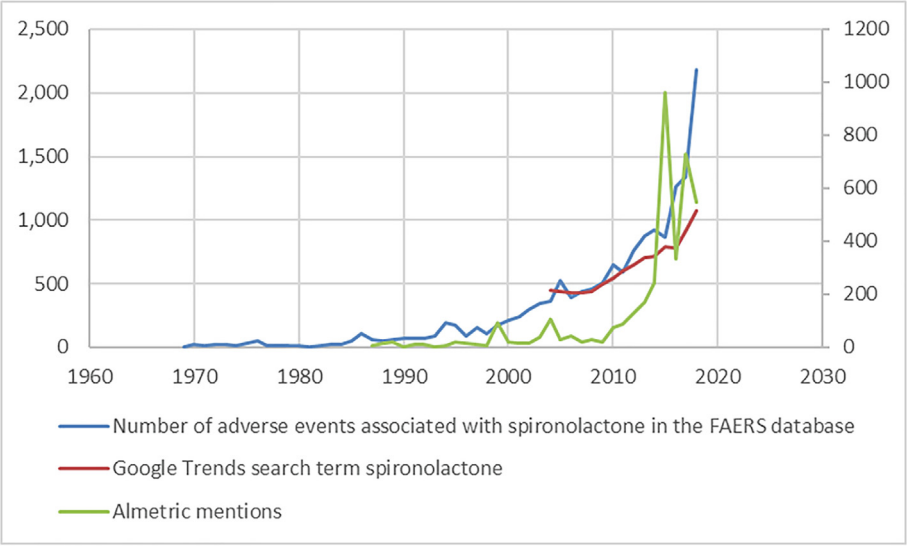

Fig. 1. Total number of adverse events associated with spironolactone for both men and women in the U.S. Food and Drug Administration Adverse Event Reporting System database by year (1969–2018), plotted with the Google Trends search term "spironolactone" by year (2004–2018) Altmetric mentions (1987–2018). Google Trends data prior to 2004 and Altmetric mentions prior to 1987 were not available.

of 112 women 18 to 45 years old (<1%) and 2 of 12 women 46 to 65 years old (16.7%). These data align well with the FAERS data, showing that the rate of hyperkalemia with spironolactone in patients aged ≤45 years is extremely low.

The increased risk of hyperkalemia in older adults is likely due to decreased kidney function with age. In a study measuring glomerular filtration rate in 159 healthy volunteers of both sexes aged 18 to 88 years, patients were divided into groups: 40 years old and younger and those 55 years old and older (Hoang et al., 2003) old and older. Patients 41 years old to 54 years old were excluded from the final analysis. The glomerular filtration rate was 22% lower in patients 55 years and older compared with those 40 years old or younger. Renal plasma flow was also decreased by 28% and glomerular hydraulic permeability by 14% in the older group versus the younger group (Hoang et al., 2003). Therefore, decreased kidney function in the older population likely increases susceptibility to hyperkalemia.

FDA indications for spironolactone are heart failure, hypertension, edema, and primary hyperaldosteronism. Based on the prescribing information recommendations, last revised in 2018, serum potassium monitoring should be performed within 1 week of initiation or titration of spironolactone, monthly for the first 3 months, quarterly for a year, and then every 6 months (Pfizer, 2018). Spironolactone is a widely used off-label treatment for acne because of its efficacy, low cost, and tolerability (Goodfellow et al., 1984; Muhlemann et al., 1986); however, there are no recommendations about potassium laboratory monitoring for this off-label use. Based on data from previous studies involving healthy women (Plovanich et al., 2015; Thiede et al., 2019), as well as our data obtained from all women in the FAERS database, hyperkalemia is very uncommon in healthy women aged ≤45 years; therefore, we suggest that serum potassium laboratory monitoring in this age group is unwarranted.

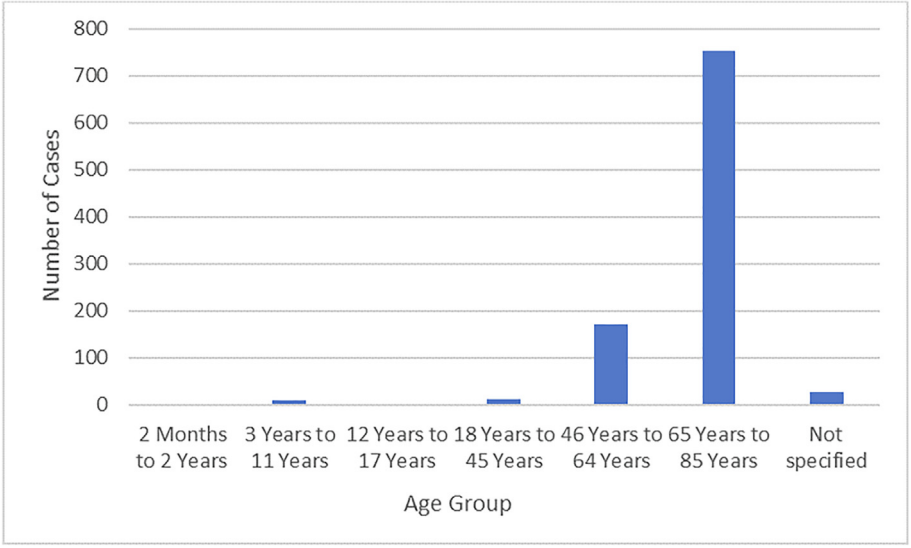

Fig. 2. Total number of hyperkalemia adverse events for women taking spironolactone, subdivided by age group (2 months to 2 years, 3–11 years, 12–17 years, 18–45 years, 46–64 years, 65–85 years, and age not specified). These age brackets were predefined in the U.S. Food and Drug Administration Adverse Event Reporting System.

A 30-day supply of 100 mg of spironolactone is $14.95 (Walmart, 2019), whereas a serum potassium level is $5.11 (Centers for Medicare and Medicaid Services, 2019), and the cost of venipuncture is $18 (Centers for Medicare and Medicaid Services, 2017). Patients who do not undergo interval laboratory testing are more likely to be compliant with therapy because they do not have to miss work or school. Nonessential laboratory testing can unnecessarily increase the composite cost of acne treatment with spironolactone. In contrast, women more than 45 years old should undergo serum potassium monitoring due to both the well-recognized age-related decline in renal function and the significantly greater risk of hyperkalemia observed in this age group.

Spironolactone has been an increasingly popular search term since 2004, as seen with Google Trends, and this increase in popularity is correlated with increased adverse event reporting to FAERS for both men and women. The increase in Altmetric mentions is also associated with increased reports of adverse reactions to the FDA for spironolactone in both sexes. Therefore, there may be increased awareness in the academic community regarding the usage and side effects of spironolactone, thus leading to more prescribing and reporting to FAERS. Since 2010, research and academic citations on spironolactone have increased yearly, resulting in a peak interest in 2015. This peak in 2015 was mostly accounted for by Antoniou et al. (2015) with an Altmetric score of 308. The authors reported that 328 of 11,968 patients of both sexes aged 66 years or older with hypertension or heart failure who died a sudden death while receiving spironolactone died within 14 days after antibiotic exposure. When compared with amoxicillin, trimethoprim-sulfamethoxazole was associated with more than a twofold increase in the risk of sudden death when taken with spironolactone due to an increased risk of hyperkalemia with the latter (Antoniou et al., 2015). This paper further supports the finding that older patients are more susceptible to hyperkalemia with spironolactone and that antibiotics, particularly trimethoprim-sulfamethoxazole, can potentiate this adverse effect.

The limitations of this study include its retrospective design, lack of FAERS data prior to January 1969, and lack of overall prescribing data for spironolactone. In addition, because FAERS data do not differentiate spironolactone as prescribed for heart failure, hypertension, edema, primary hyperaldosteronism, or acne, our study could not control for these and other confounding comorbidities or associated therapies. Because data in FAERS are reported by patients, health care providers, and pharmaceutical companies, the adverse effects have not been confirmed by other means. Furthermore, our Altmetric search included worldwide data, but 85% of publications originated in the United States, and the Google Trends data included only U.S. data, which slightly biases the comparison.

For future studies, it is important to analyze drug interactions more carefully to determine which other medications may potentiate the risk for hyperkalemia in patients taking spironolactone. It is also important to quantitate overall U.S. prescription data to better understand the relative frequency of these adverse effects reported to the FDA.

Conclusion

In this study, we found that in women of all ages taking spironolactone for any indication, hyperkalemia is the most common adverse effect reported in the FAERS database. However, it is important to note that hyperkalemia is exceptionally uncommon in women 45 years old and younger. Therefore, in the absence of risk factors for hyperkalemia or reduced renal function, potassium laboratory monitoring is unnecessary in younger women taking spironolactone. The incidence of hyperkalemia observed in women taking spironolactone increases with age; therefore, interval laboratory monitoring is recommended for women aged >45 years. A review of concomitant medications is essential to avoid prescribing spironolactone with drugs that may also increase serum potassium levels, such as antibiotics, particularly trimethoprim-sulfamethoxazole.

Conflict of Interest

None.

Funding

None.

Study Approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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