SHORT COMMUNICATION

Drug Safety 2007; 30 (12): 1143-1149
0114-5916/07/0012-1143/$44.95/0

Detection of Spironolactone-Associated Hyperkalaemia Following the Randomized Aldactone Evaluation Study (RALES)

Manfred Hauben,[1,2,3,4] *Lester Reich*,[1] *Charles M. Gerrits*[5] and *David Madigan*[6]

1 Risk Management Strategy, Pfizer Inc., New York, New York, USA
2 Department of Medicine, New York University School of Medicine, New York, New York, USA
3 Department of Pharmacology and Department of Community and Preventive Medicine, New York Medical College, Valhalla, New York, USA
4 School of Information, Computing, and Mathematics, Brunel University, London, UK
5 Department of Global Pharmacoepidemiology and Outcomes Research, Takeda Global R&D Center Inc., Lincolnshire, Illinois, USA
6 Department of Statistics, Rutgers University, Piscataway, New Jersey, USA

Abstract

Introduction: A population-based analysis has suggested that the publication of the RALES (Randomized Aldactone Evaluation Study) in late 1999 was associated with both the wider use of spironolactone to treat heart failure and a corresponding increase in hyperkalaemia-associated morbidity and mortality in patients also being treated with ACE inhibitors.

Objectives: To gain further insight into the reporting of spironolactone-associated hyperkalaemia in an independent dataset by analysing the spontaneous reporting experience in relation to the publication of RALES, and to determine whether the implementation of a commonly used data mining algorithm (DMA) might have directed the attention of safety reviewers to the spironolactone/hyperkalaemia association in advance of epidemiological findings.

Methods: We calculated the reporting rate of spironolactone-associated hyperkalaemia per 1000 reports per year from 1970 through to the end of 2005 by identifying relevant cases in the US FDA Adverse Event Reporting System. We did this for reports of spironolactone-associated hyperkalaemia (where spironolactone was listed as a suspect drug) and according to whether the reports listed an ACE inhibitor as a co-suspect or concomitant medication. A further statistical analysis of the overall reporting of spironolactone (suspect drug)-associated hyperkalaemia was also performed. We also performed 3-dimensional (3-D; drug-drug-event) disproportionality analyses using a DMA known as the multi-item gamma-Poisson shrinker, which allows the calculation and display of a 3-D disproportionality metric known as the 'interaction signal score' (INTSS). This

metric is a measure of the strength of a higher order reporting relationship of a triplet (i.e. drug-drug-event) association above and beyond what would be expected from the largest disproportionalities associated with the individual 2-way associations.

Results: Visual inspection of a graph of the reporting frequency of spironolactone (suspect drug)-associated hyperkalaemia per 1000 reports was highly suggestive of a change point. The t-test on the arcsine-transformed data showed a significant difference in reporting of spironolactone-hyperkalaemia combination through 1999 compared with 2000 onwards ($p < 0.001$). When examining the reporting time trends according to the presence or absence of an ACE inhibitor, the change point seemed to be mostly attributable to an increase in the number of spironolactone (suspect drug)-associated hyperkalaemia reports with ACE inhibitors listed as a co-suspect drug. No obvious change points in INTSSs for spironolactone-ACE inhibitor-hyperkalaemia reports were observed.

Discussion: Although we could not pinpoint the relative contribution of many possible artifacts in the reporting process, as well as increased drug exposure, increased adverse event incidence and/or a change in patient monitoring practices, to our findings, we observed a notable change in reporting frequency of spironolactone-associated hyperkalaemia in temporal proximity to the publication of RALES. Evidence of this was provided by a trend analysis depicted in a simple graph that was supported by statistical analysis. The observed trend was in large part due to increased reporting of spironolactone-associated hyperkalaemia with reported co-medication with ACE inhibitors.

Conclusion: These findings are consistent with those originally reported in an epidemiological analysis. In this retrospective exercise, a simple graph was more illuminating than more complex data mining analyses.

Introduction

A primary objective of pharmacovigilance is the timely identification of adverse events that are novel by virtue of their clinical nature, severity and/or frequency. Pharmacovigilance is rather distinctive among public health surveillance activities in terms of the wide range of events under scrutiny. It therefore entails the use of multiple data streams and methods, which may be described as a teleoanalytical approach.[1]

A population-based analysis by Juurlink and colleagues[2] has suggested that the publication of RALES (the Randomized Aldactone Evaluation Study)[3] in late 1999 was associated with both the wider use of spironolactone to treat heart failure and a corresponding increase in hyperkalaemia-associated morbidity and mortality in patients being treated with ACE inhibitors.[2]

Objectives

Our aims were to (i) gain further insight into the reporting of spironolactone and hyperkalaemia in an independent dataset by analysing the spontaneous reporting experience in relation to the publication of RALES; and (ii) determine whether the implementation of a commonly used data mining algorithm (DMA) might have directed the attention of safety reviewers to the spironolactone/hyperkalaemia association in advance of the epidemiological findings.

Methods

We calculated the reporting rate of spironolactone-associated hyperkalaemia per 1000 reports per year from 1970 through to the end of 2005 by identifying relevant cases in the US FDA Adverse Event Reporting System (AERS), obtained through the *Freedom of Information Act*, 1966. We did this

for reports (where spironolactone was listed as a suspect drug) of spironolactone-associated hyperkalaemia and according to whether the case details for the reports listed an ACE inhibitor as a co-suspect or concomitant medication. The data were pre-processed by the data mining vendor (Lincoln Technologies, Waltham, MA, USA) according to their protocol to standardise drug nomenclature/event terms and reduce duplicate reports. For duplicate cases with the same manufacturer's case identification number, only the latest report was retained by the vendor. The reporting rate of spironolactone-associated hyperkalaemia per 1000 cases per year in the AERS database through 2005 was calculated as the number of reports of hyperkalaemia in the vendor's database listing spironolactone as a suspect drug, divided by the total number of reports. Time subsetting was by year of report to the FDA.

We performed a statistical analysis of the overall reported proportion of all reports of hyperkalaemia listing spironolactone as a suspect drug to explore this further. Because of the limited number of observations after the potential change point (i.e. the publication of RALES in 1999) and a lack of significant auto-correlation (i.e. correlation between successive values in time) according to a Durbin-Watson test, an unequal variances t-test was applied to the arcsine-transformed data. The arcsine transformation[4] is commonly used to help decouple the actual value of a score from its variance.

We also performed four separate 3-dimensional (3-D; i.e. drug-drug-event) disproportionality analyses using a DMA known as the multi-item gamma-Poisson shrinker (MGPS; WebVDME version 5.2, build 146, Lincoln Technologies).[5] Specifically we computed a 3-D disproportionality metric known as the 'interaction signal score' (INTSS). This metric measures the strength (e.g. how disproportionately frequent the reporting frequency is) of a higher order (i.e. drug-drug-event) association above and beyond that which would be expected from the largest disproportionalities associated with the individual 2-way associations. The INTSS is defined as EB_{05}/EB_{95}MAX, where the EB_{05} is the conservative estimate score for the full 3-D combination (drug-drug-event; or triplet) and the EB_{95}MAX is the highest EB_{95} score found for the individual pairs in the triplet (e.g. drug 1-event, drug 2-event). Empirical Bayesian metrics are explained in more detail in previously published papers.[6,7] A triplet might normally be considered interesting if the INTSS is >1; this is known as a signal of disproportionate reporting (SDR). The 3-D analyses were performed using both a year-on-year analysis (the DMA was applied to the data for each year individually), as well as cumulative subsetting by year (the analysis by year included that year as well as previous years) through the fourth quarter of 2005 for a total of four analyses (two for suspect drugs and two for suspect-plus-concomitant drugs). For the suspect drug analysis, the data mining run was configured to include only suspect drugs as the items to be available for analysis. For the suspect-plus-concomitant drug analysis, both suspect and concomitant drugs were available. Stratification by age, gender and FDA year of report was also used. A case count threshold of three was used to accommodate the computational intensity of this higher order analysis so that the data mining runs could be successfully completed.

Results

Visual inspection of a graph of the reporting frequency of spironolactone (suspect drug)-associated hyperkalaemia per 1000 reports in AERS was highly suggestive of a change point (figure 1). The t-test on the arcsine-transformed data showed a significant difference in reporting of the spironolactone-hyperkalaemia combination from 1970 through to the end of 1999 compared with that in 2000 onwards ($p < 0.001$). When examining the reporting time trends according to the presence or absence of an ACE inhibitor as a co-suspect or concomitant drug, the change point seemed to be mostly attributable to an increase in the number of spironolactone (suspect drug)-associated hyperkalaemia reports in which ACE inhibitors were listed as a co-suspect drug (figures 2 and 3).

No obvious change points in INTSS were observed for spironolactone-ACE inhibitor-hyperkalaemia reports in either the cumulatively subsetted data

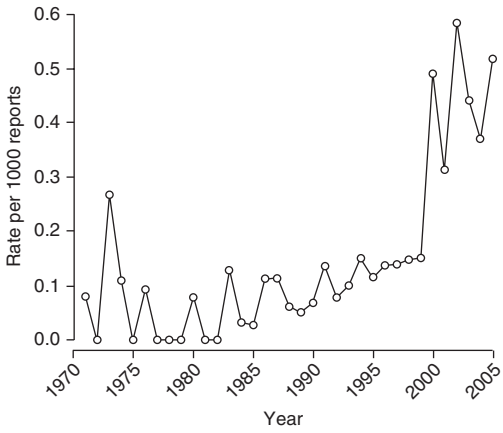

Fig. 1. Spironolactone (suspect drug)-associated hyperkalaemia reporting rate (1970–2005).

mining run that was configured to include suspect drugs or the run that was configured to include suspect-plus-concomitant drugs. As an example of this, findings for three ACE inhibitors (concomitant captopril, enalapril or lisinopril) for the time period 1996–2002 are provided in figure 4. Data were also available for benazepril, fosinopril, perindopril, quinapril, ramipril and trandolapril, but were not inclusive of the years 1996–2002. For these latter drugs in the years after 1996 when there were data, the INTSS was always <1 for both the suspect and suspect-plus-concomitant cumulative analyses. The results of the two, year-on-year, 3-D data mining analyses were 'patchy' in that there were no new reports (or one to two reports, which were not documented because we had to opt for a case count threshold of three) for some years, and this complicated interpretation. Thus, these calculations would probably not have directed the attention of safety reviewers to a possible increase in the reporting of spironolactone-ACE inhibitor-associated hyperkalaemia.

An interesting ancillary observation was that, for captopril, INTSS values were higher in the suspect-drug analysis than in the suspect-plus-concomitant analysis. They were consistently <1 (range 0.71–0.88) for the suspect-plus-concomitant analysis (figure 4) and consistently >1 (range 1.16–1.55) for the suspect-drug analysis for the years examined (1996–2002).

Discussion

The relative contribution of the many possible artifacts to our findings cannot be pinpointed, including those arising from differences in the reporting process, as well as increased drug exposure, exposure to other drugs that might impact potassium balance (e.g. angiotensin receptor blockers, potassium supplements, loop diuretics), increased adverse event incidence, and/or a change in patient monitoring practices.[8,9] However, we observed a notable change in reporting frequency of spironolactone-associated hyperkalaemia in temporal proximity to the publication of RALES, as evidenced by a trend analysis depicted in a simple graph (figure 1) that was supported by statistical analysis. This was in large part due to increased reporting of spironolactone-associated hyperkalaemia with reported co-medication with ACE inhibitors. These findings are consistent with those originally reported in an epidemiological analysis.[2]

In addition to our objective of gaining insight into the reporting of spironolactone-associated hyperkalaemia and its relationship to the publication of RALES, another stated objective was to assess whether the methodology chosen in our study, ap-

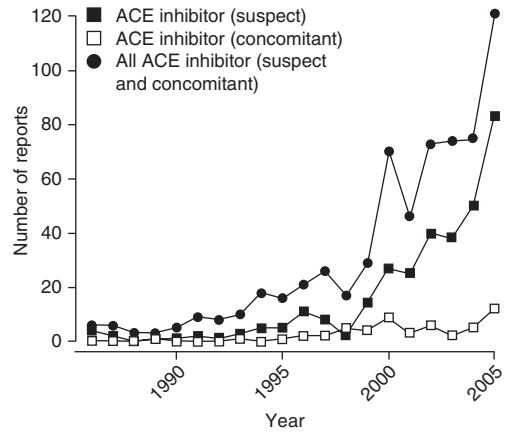

Fig. 2. Spironolactone (suspect drug)-associated hyperkalaemia number of reports by year with and without ACE inhibitor reported as co-medication (suspect or concomitant drug) and overall.

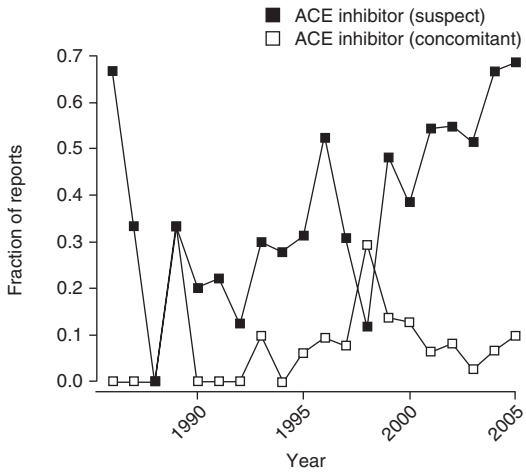

Fig. 3. Fraction of spironolactone (suspect drug)-associated hyperkalaemia reports with ACE inhibitors (suspect or concomitant).

plied to spontaneous reporting system (SRS) data, might have drawn the attention of safety reviewers to this issue prior to the initial epidemiological study. Although it is obviously impossible to definitively say how any given safety reviewer would have interpreted or acted upon these findings, one typical implementation of a 3-D data mining analysis would probably not have directed attention to a similar potential association in AERS data. Given the way the INTSS is calculated, the lack of an SDR is not surprising given our previous report of persistently high levels of disproportionate reporting of hyperkalaemia (a labelled event in the product literature for spironolactone) for all 35 years of available data.[10] This may have contributed to a failure to detect a change in the reporting of this combination subsequent to the publication of RALES, using routine implementations of both a non-Bayesian (i.e. proportional reporting ratios [PRRs]) and an empirical Bayesian (i.e. MGPS) 2-D (drug-adverse event) disproportionality analysis, although certain related events that could represent epiphenomena of hyperkalaemia had *de novo* disproportionate PRRs. Interestingly, since disproportionality analysis may be fairly robust to overall secular reporting trends for drugs (as opposed to specific drug-event combinations), a general reporting stimulus for a drug might not significantly affect the patterns of SDRs observed. We also reported an increase in the crude reporting frequency of spironolactone (suspect drug)-associated hyperkalaemia in the year following the publication of RALES that seemed qualitatively distinctive.[10]

One possible limitation of our analysis is that we did not also subset our timeframes by date of event, which was available for 88.6% of the hyperkalaemia cases. Results might have been different under those circumstances, although it should be noted that the event date was provided at the case level and not at the event level. Another limitation is that we did not systematically analyse for 'notoriety bias',[11] i.e. that the post-change-point cases were not largely old cases, whose delayed reporting was due to notoriety/publicity resulting from the publication of RALES. We did, however, visually inspect all spironolactone (suspect drug)-associated hyperkalaemia cases with an FDA date of 1999 or later, and on review, we largely excluded this kind of reporting artifact. Thirdly, our need to opt for a case count threshold of three had the effect of restricting the database analysis, and this is one of many situation-specific factors that could affect the output of DMAs.

The higher INTSS obtained for captopril with the data mining run that was configured to include suspect drugs compared with the data mining run that

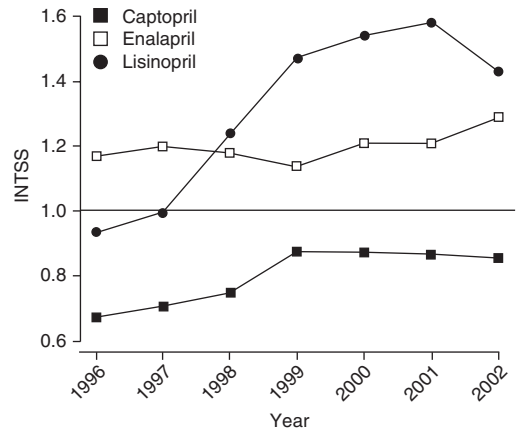

Fig. 4. Interaction signal scores (INTSS) for spironolactone plus selected ACE inhibitors by year for the period 1996–2002 (suspect drug plus concomitant drug data mining analysis).

was configured to include suspect-plus-concomitant drugs was an interesting finding. Discussions at scientific sessions on data mining suggest that suspect-plus-concomitant drug data mining analysis is the preferred strategy for potential drug-drug interactions. While the latter is intuitively appealing and may be true on balance, we have noted a tendency to make generalisations in data mining based on anecdote, conjecture, plausibility arguments and/or personal bias. In fact, it is often difficult to predict the full range of effects of the numerous choices available in data mining and the 'law of unanticipated results' should always be borne in mind.

The natural questions to ask are how typical are such persistent and high SDRs for labelled events and what is the predictive value of such observations for identifying ongoing safety issues? We are not aware of any systematic study of this phenomenon. Although spironolactone may not be typical of all drugs with respect to the complexity/noncomplexity of its adverse-event profile, we have anecdotally observed significant persistent SDRs for labelled events with various other drugs in cumulatively subsetted data as well, although we have not studied this systematically. Year-on-year analyses could be useful in this regard for detecting conspicuous changes in reporting of labelled events, which show persistent disproportionate reporting in cumulatively subsetted data.

While the discovery of novel adverse events appropriately receives considerable attention, Strom[12] has pointed out that detecting new aspects of known events is of major importance in drug safety and that this may not be a strength of SRS data regardless of which of the currently available methods is applied, although a recent retrospective study reported that disproportionality analysis of SRS data may have value in this context.[13] Further research on the application of data mining for the discovery of new aspects of labelled events may improve our ability to detect the full range of such phenomena.[14] Regarding the specific issue of increased frequency of reporting, the FDA revoked the regulatory requirement for expedited increased frequency reporting in 1997 because historical experience indicated that it had not contributed to the timely identification of actionable safety problems beyond that of other required but non-expedited safety reports.[15]

Bate and Edwards[16] have noted the extremes of opinions about data mining in pharmacovigilance, from "unbridled optimism" to "considerable scepticism." Emphasising only the positive aspects, while down-playing associated difficulties and limitations, could be of potential detriment to patient safety. The singular range and variety of events of interest in pharmacovigilance requires a flexible, multifactorial and holistic approach to safety surveillance.

Conclusion

In this retrospective exercise, a simple graph was more illuminating than more complex data mining analysis. This is one example. The opposite may be true in other pharmacovigilance scenarios.

Acknowledgements

No sources of funding were used to assist in the preparation of this article.

Dr Hauben is an employee of and owns stock options and shares in Pfizer, the manufacturer of spironolactone and some ACE inhibitors included in this study, and holds stock in other pharmaceutical companies that may market ACE inhibitors. Dr Reich is an employee of Pfizer. Drs Gerrits and Madigan have no conflicts of interest that are directly relevant to the contents of this article.

References

1. Wald NJ, Morris JK. Teleoanalysis: combining data from different types of study. BMJ 2003; 327: 616-8
2. Juurlink DM, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351 (6): 543-51
3. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341: 709-17
4. Zar JH. Biostatistical analysis. 4th rev. ed. Upper Saddle River (NJ): Prentice-Hall, 1998
5. DuMouchel W, Pregibon D. Empirical Bayes screening for multi-item associations. In: Proceedings of the ACM Conference on Knowledge Discovery and Data Mining 2001 Aug 26-29; San Francisco (CA): 67-76
6. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system (with discussion). Am Stat 1999; 53 (3): 177-202

7. Hauben M, Madigan D, Gerrits CM, et al. The role of data mining in pharmacovigilance. Expert Opin Drug Saf 2005; 4 (5): 929-48
8. Besancon JF, Lagarce L, Laine-Cessac P, et al. Biological survey in patients treated with the combination spironolactone and angiotensin converting enzyme inhibitor: a population-based analysis. Drug Saf 2006; 29 (10): 929
9. Raebel MA, McClure DL, Chan AK. Laboratory evaluation of potassium and creatinine among ambulatory patients prescribed spironolactone: are we monitoring for hyperkalemia? Ann Pharmacother 2007; 41 (2): 193-200
10. Hauben M, Reich L, Gerrits CM. Reports of hyperkalemia after publication of RALES: a pharmacovigilance study. Pharmacoepidemiol Drug Saf 2006; 15 (11): 775-83
11. Moore N, Hall G, Sturkenboom M, et al. Biases affecting the proportional reporting ratio (PRR) in spontaneous reports pharmacovigilance databases: the example of sertindole. Pharmacoepidemiol Drug Saf 2003; 12 (4): 271-81
12. Strom BL. Potential for conflict of interest in the evaluation of suspected adverse drug reactions a counterpoint. JAMA 2004; 292 (21): 2643-6
13. Hochberg AM, Reisinger SJ, Pearson RK, et al. Using data mining to predict safety actions from FDA adverse event reporting system data. Drug Inf J 2007; 41: 633-43
14. Orre R, Bate A, Noren GN, et al. A Bayesian recurrent neural network for unsupervised pattern recognition in large incomplete data sets. Int J Neural Syst 2005; 15 (3): 207-22
15. Department of Health and Human Services. Food and Drug Administration 21 CFR Parts 310, 314, and 600 postmarketing expedited adverse experience reporting for human drug and licensed biological products. Increased Frequency Reports Federal Register 1997 Jun 25; 62 (122): 34166-8
16. Bate A, Edwards IR. Data mining in spontaneous reports. Basic Clin Pharmacol Toxicol 2006; 98 (3): 324-30

Correspondence: Dr *Lester Reich*, Risk Management Strategy, Pfizer Inc., 235 E. 42nd St, New York, NY 10017, USA. E-mail: Lester.Reich@Pfizer.com