Critical Appraisal

Hyperkalemia associated with spironolactone therapy

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Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.

Research question

What were the trends in spironolactone prescriptions and hyperkalemia-associated hospitalization and death before and after publication of the Randomized Aldactone Evaluation Study (RALES)? The RALES established spironolactone therapy's clinical benefit for patients with severe heart failure.

Type of article and design

Population-based time-series analysis of administrative health care databases in Ontario.

Relevance to family physicians

Heart failure is common; it affects nearly one in 10 people older than 65.[1] Effective treatment reduces symptoms and hospitalizations and allows patients to keep active. Drug therapy is a critical component of heart failure treatment. The RALES, published in 1999, demonstrated that adding spironolactone to standard therapy reduced morbidity and mortality among patients with severe heart failure (35% death rate in the spironolactone group, and 46% death rate in the placebo group; relative risk of death 0.70, 95% confidence interval [CI] 0.60 to 0.82).[2]

During the last decade, heart failure treatment guidelines reduced the role of diuretics and digoxin and emphasized angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and angiotension-2 receptor blockers (ARBs).[1] Hyperkalemia is a known side effect of ACE inhibitors and ARBs, but is uncommon in patients without such risk factors as diabetes or impaired renal function. Combination therapy with ACE inhibitors and ARBs with the addition of potassium-sparing diuretics further increases risk of hyperkalemia.[3]

Overview of study and outcomes

The Ontario Drug Benefit (ODB) prescription database (1994 through 2001) was used to identify patients receiving prescriptions for spironolactone or other drugs known to increase potassium levels. Hospital admissions involving hyperkalemia or heart failure (including death) were obtained from the Canadian Institute for Health Information's Discharge Abstract Database for the same period. Drug prescribing and hospitalization rates were calculated for three 4-month periods each year. A time-series analysis compared the predicted pattern of

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drug prescriptions and hospital admissions involving hyperkalemia with the actual pattern observed during each period. Primary analysis looked at spironolactone prescriptions and rates of hospital admission for hyperkalemia or heart failure among patients receiving ACE inhibitors who had been hospitalized for heart failure in the past 3 years. Secondary analysis looked at these rates among all patients receiving ACE inhibitors, regardless of history of heart failure.

Results

Patients with heart failure. Before the RALES trial, the prescription rate for spironolactone for patients taking ACE inhibitors was steady at about 30/1000 patients in 1999. After publication of the RALES trial, spironolactone prescriptions jumped fivefold to 149/1000 patients by the end of 2001 ($P < .001$ compared with the earlier period), with a median dose of 25 mg daily.

Hospital admissions for hyperkalemia had been climbing slowly from 1994 (2.4/1000) through 1999 (4.0/1000), but increased nearly threefold to 11/1000 by late 2001 ($P < .001$). The rate of hyperkalemia associated with in-hospital death rose gradually between 1994 (0.3/1000) and 1999 (0.7/1000), but increased nearly threefold after publication of the RALES to 2.0/1000 in late 2001 ($P < .001$). Patients treated with spironolactone were on average 13 years older than patients in the RALES. There were equal numbers of men and women. Most patients were also taking loop diuretics, and more than half had been hospitalized for heart failure within the previous month.

Prescription patterns for other drugs that could influence risk of hyperkalemia (eg, loop diuretics, beta-blockers, and nonsteroidal anti-inflammatory drugs) were examined. No substantial changes in outcome were noted when the analyses were adjusted for use of these agents.

For patients with heart failure, comparison of actual and predicted number of events found that publication of the RALES was associated with 560 excess hyperkalemia-related hospitalizations (95% CI 285 to 754) and 73 (95% CI 27 to 120) excess in-hospital deaths in Ontario in 2001.

All patients taking ACE inhibitors. In all patients dispensed ACE inhibitors (including those who had not been hospitalized previously for heart failure), prescription rates for spironolactone increased almost threefold after publication of the RALES from 12/1000 in early 1999 to 32/1000 by late 2001. Hospital admissions for hyperkalemia increased after the trial from 1.2/1000 in 1999 to 2.8/1000 in 2001 ($P < .001$). In-hospital hyperkalemia-associated death followed a similar pattern to that of the heart-failure patients, gradually increasing from 1994 (0.10/1000) through 1999 (0.17/1000) and then approximately doubling by late 2001 to 0.39/1000 ($P < .001$). Rates of hospitalization for heart failure or death from any cause declined slightly over time; no statistically significant differences in rates were observed after publication of the RALES.

In the "all patients" group, a comparison of actual and predicted number of events found that publication of the RALES was associated with 1485 excess hyperkalemia-related hospitalizations (95% CI 1150 to 1802) and 171 (95% CI 129 to 219) excess in-hospital deaths in Ontario in 2001.

Other observations. No difference in study outcomes was found for patients who were or were not taking beta-blockers. The authors examined whether there was an increased rate of survival among patients, and if this could have influenced the observations. Publication of the RALES was not associated with an increase in chronic diseases but was associated with a statistically significant increase in hospital admissions for renal insufficiency.

Analysis of methodology

This retrospective, population-based, time-series analysis studied a representative Canadian sample of patients taking spironolactone. The strength of population-based time series is that they eliminate the possibility of measurement bias (ie, outcomes and exposures should have been measured consistently before and after the RALES period). The overall error rate of the databases is reported to be low with an expected rate of 1% in the ODB database. The accuracy of coding in the hospitalization database for all diagnoses is not known, but is cited as very high for heart failure (90% to 96%).

Weaknesses of population-based time-series analyses include a lack of direct patient data, in this case, measurements of serum creatinine or potassium levels that could be linked with medication use and hospitalization for hyperkalemia. Medication compliance was not evaluated, only dispensing patterns. Patterns of compliance would not be expected to change dramatically during the study period. Also, these types of studies are susceptible to unmeasured and unidentified confounding variables. Complex statistical techniques were used to examine and correct for known potential confounders, but unknown confounders could exist. Consequently, causality is implied but not established.

Despite the limitations of observational studies based on administrative data, this study presents a compelling case that a relationship exists between publication of the RALES and increases in use of spironolactone and hospital admissions for hyperkalemia at the population level. This study cannot provide evidence of true cause and effect because of the nature of its design. It is important to note that, because this study focused on patients in the ODB database, its observations might not apply to younger patients with fewer risk factors for hyperkalemia.

Application to clinical practice

This trial highlights the risk of applying trial results based on specific, restricted, well-monitored patient populations to broader, less representative populations who might be at greater risk of adverse events and would be less likely to have the level of monitoring dictated by a stringent study protocol. In the RALES, potassium was monitored every 4 weeks for the first 12 weeks, every 3 months up to 1 year, and then every 6 months thereafter. Serum potassium was measured again at week 9 if the dose of spironolactone had increased to 50 mg daily.

Aldosterone receptor blockade by spironolactone reduced morbidity and mortality among heart failure patients in the population studied in the RALES trial, but the risks of hyperkalemia appear to be higher in general practice. Spironolactone remains an important treatment for heart failure in patients who are likely to obtain a clinically significant benefit, who can have their concomitant risk of hyperkalemia managed, and who can undergo regular monitoring.

Some specific strategies can be considered in primary care to support best practice for spironolactone use.

- Use a preplanned potassium monitoring schedule and laboratory requisitions for all patients newly starting spironolactone.
- Remind all patients taking spironolactone about laboratory visits.
- Screen the charts of patients with heart failure and patients who are taking spironolactone to find those lacking recent reports of potassium levels.
- Review use and monitoring of spironolactone during continuing medical education or administrative meetings.
- Partner with local pharmacies to identify patients taking spironolactone and determine a mechanism for reviewing spironolactone use and monitoring potassium levels regularly.
- Provide patient education materials that reinforce the usefulness of regular potassium monitoring.

Bottom line

- Publication of the RALES in 1999 was associated with rapid increases in prescriptions for spironolactone and in hyperkalemia-associated

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hospitalizations and in-hospital hyperkalemia-associated death. This is partly due to applying clinical trial data to populations that differ from those studied or that are outside the close scrutiny of a clinical trial setting. These data reflect the marked effect a well publicized clinical trial can have on prescribing patterns, even in the absence of promotion by pharmaceutical manufacturers. Spironolactone was available in generic form before and after the RALES was published.

- Spironolactone should be used judiciously for patients at risk of hyperkalemia (concurrent use of nonsteroidal anti-inflammatory drugs, beta-blockers, or ACE inhibitors, or presence of diabetes or renal dysfunction).
- Spironolactone should be reserved for patients with New York Heart Association class III or IV heart failure with severe left ventricular systolic dysfunction (ejection fraction of no more than 35%). Spironolactone might not be appropriate for patients with mild-to-moderate left ventricular systolic dysfunction, diastolic dysfunction, or cor pulmonale.
- Patients taking spironolactone require regular monitoring of potassium levels and renal function.

References

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Points saillants

- La publication des résultats de l'étude RALES en 1999 a été associée à une augmentation rapide des ordonnances de spironolactone, ainsi que des hospitalisations pour cause d'hyperkaliémie et des décès reliés à l'hyperkaliémie dans les hôpitaux. Cela est partiellement attribuable à l'application de données tirées d'études cliniques à des populations qui diffèrent de celles étudiées ou qui ne faisaient pas l'objet de la surveillance étroite exercée dans un environnement d'étude clinique. Ces données font valoir l'influence marquée que peut avoir sur les habitudes d'ordonnance une étude clinique ayant fait l'objet de grande publicité, même en l'absence de promotion de la part des fabricants de produits pharmaceutiques. La spironolactone était disponible sous forme générique avant et après la publication de l'étude RALES.
- La spironolactone devrait être utilisée judicieusement chez les patients à risque d'hyperkaliémie (usage concomitant d'anti-inflammatoires non stéroïdiens, de bêtabloquants ou d'inhibiteurs de l'enzyme de conversion de l'angiotensine, ou présence de diabète ou de dysfonction rénale).
- L'administration de la spironolactone devrait être limitée aux patients souffrant d'insuffisance cardiaque de classe III ou IV, selon la New York Heart Association, ayant une dysfonction systolique ventriculaire gauche grave (fraction d'éjection ne dépassant pas 35%). La spironolactone pourrait ne pas être indiquée chez les patients ayant une dysfonction systolique ventriculaire gauche de légère à modérée, une dysfonction diastolique ou un cœur pulmonaire.
- Il faut exercer une surveillance régulière des niveaux de potassium et de la fonction rénale chez les patients qui prennent de la spironolactone.