Long term therapy with spironolactone

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Abstract
Objective: to evaluate the duration of therapy with spironolactone in daily practice.
Method: a retrospective follow-up of a cohort of patients with a first prescription for spironolactone between January 1, 1990 and December 31, 1996 and at least one hospital discharge for CHF in the preceding year.
Results: 243 patients met the inclusion criteria and were followed until the end of data collection. The average starting dosage of spironolactone was 55 mg. 143 patients (58.8%) discontinued spironolactone therapy before the end of follow-up. 98 patients (40.8%) discontinued within 6 months of follow-up. Of the 137 patients (56.4%) who did use spironolactone and an ACE-inhibitor concomitantly, only 45 (32.8%) continued this combination until the end of follow-up. The remainder of the patients discontinued either the ACE-inhibitor (10.9%) or spironolactone (12.4%) or both (43.8%).
Conclusion: while the reasons for discontinuation remain unclear, our data suggest that it is difficult to keep patients on both drugs. It is not certain whether these findings from past spironolactone use can be extrapolated to future use. Patients in the general population received higher average spironolactone dosages compared to the RALES study (55 mg vs. 26 mg), possibly resulting in more adverse effects and partly explaining the high discontinuation rate.

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Introduction

In August 1999 the results of the Randomised Aldactone Evaluation Study (RALES) were released electronically ahead of a publication in the New England Journal of Medicine on September 3 1999 [1]. RALES was an adequately designed trial to study the effects of spironolactone in patients with congestive heart failure (CHF). It suggested that patients with advanced heart failure should preferably be treated with an Angiotensin Converting Enzyme (ACE)-inhibitor in combination with spironolactone.

This publication was accompanied by extensive media coverage and led to an increase in spironolactone prescriptions in patients with severe congestive heart failure.

The study results suggested that patients benefit mainly from long-term use of spironolactone (mean follow-up in RALES was 24 months). However, spironolactone use has both bothersome (e.g. gynaecomastia; 10% of men in RALES) and serious (e.g. hyperkalemia and renal disturbances) side effects. Notably the combination with ACE-inhibitors can lead to severe hyperkalemia and renal dysfunction [2]. In RALES, patients with already high serum potassium or creatinine were excluded. Moreover, serum potassium and kidney function was measured every 4 weeks during the first 12 weeks and every 3 months thereafter for up to 1 year. Literature also suggests that a combination of ACE-inhibitors and spironolactone is feasible provided that renal function is normal and serum potassium concentration is closely monitored [3]. Patients using this combination of ACE-inhibitors might develop serious renal dysfunction and hyperkalemia when they are not monitored regularly. This could lead to premature termination of therapy. Furthermore, discontinuation rates of new therapies and especially cardiovascular medications in the general population are reported to be high [4-6]. This could also contribute to a sub-optimal duration of therapy with spironolactone. Indications for the favourable effects of spironolactone in patients with CHF has been available for several years [7-9]. Therefore spironolactone was already used in patients with advanced CHF (e.g. NYHA class III-IV), matching the study population of RALES. We studied a cohort of CHF-patients who received a first prescription for spironolactone in order to evaluate the duration of spironolactone therapy in these patients.

Method

Data were used from the Pharmo ongoing record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined 300,000 residents population of 6 medium-sized cities in the Netherlands [10].

Medication histories and hospital data were collected from 1990 to 1999. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification [11]. Hospital discharge records were coded according to the International Classification of Diseases, 9th Edition (ICD-9). Clinical modification codes were also utilised.

We included a cohort of patients with a first-time prescription for spironolactone in the period from January 1, 1990 until December 31, 1996 and at least one primary hospital discharge for CHF in the preceding year. We detected 2024 patients with a primary hospital discharge for CHF. Of these patients 316 received a prescription for spironolactone within one year after hospital discharge. Of the latter we had a follow-up of at least 6 months for 243 patients. These 243 patients were followed until the end of data collection (June 30, 1999) or until their disappearance from the database, indicating a move to a city outside the scope of Pharmo, institutionalisation or death.

The discontinuation of spironolactone or ACE-inhibitors was defined as the absence of dispensing of either spironolactone or an ACE-inhibitor by the pharmacist, in the presence of other drug-dispensing for at least 6 months.

Duration of therapy was determined by dividing the number of dispensed doses by the dosage regimen. A simultaneous start was defined as the start of an ACE-inhibitor and spironolactone on the same day.

Results

We identified 243 patients who met inclusion criteria. Basic characteristics of the patients are given in Table 1. Patients were predominantly older than 70 years. There was an equal distribution among sexes and a broad use of co-medication.

We found that 143 patients (58.8%) discontinued spironolactone therapy before the end of follow-up (Table 2). 98 patients (40.8%) discontinued within 6 months of follow-up.

Furthermore, we saw that 106 patients (43.6%) received no ACE-inhibitor prescription together with spironolactone. Of the 137 patients (56.4%) who did use spironolactone and an ACE-inhibitor concomitantly, only 45 (32.8%) continued this combination until the end of follow-up. The remainder of the patients discontinued either the ACE-inhibitor (10.9%) or spironolactone (12.4%) or both (43.8%).

Discussion

Basic characteristics of the patients were slightly different from the RALES population. Patients were older and our cohort consisted of a higher percentage of women (Table 2). The differences in basic characteristics may be due to the fact that patients admitted to clinical trials in Congestive Heart Failure tend to include relatively more young and healthy men [12]. Differences in medication use can be partly explained by regional differences [13]. The use of loop diuretics

Table 1 *Comparison of characteristics of patients in this study with the RALES population*

	This study	*RALES*
Study design	*Observational*	*Randomised controlled trial*
Setting	*Netherlands*	*195 centres in 15 countries*
No. of patients receiving spironolactone	243	822
Sex		
Male	123 (50.6%)	603 (73%)
Female	120 (49.4%)	219 (27%)
Average age	72.6 yr.	65 yr.
Age distribution		
<60	24 (9.9%)	not given
60-70	56 (23.0%)	
70-80	99 (40.7%)	
80-90	64 (26.3%)	
Comedication at start of spironolactone		
loop diuretics	231 (95.0%)	100 %
ACE-inhibitors	146 (60.1%)	95 %
digoxin	127 (52.3%)	75 %
acetylsalicylic acid	49 (20.2%)	36 %
oral anticoagulants	134 (55.1%)	not given
potassium supplements	22 (9.1%)	29 %
betablockers	40 (16.5%)	11 %

Table 2 *Follow-up of patients with severe heart failure who were prescribed spironolactone between 1990-1996*

	N = 243
Use of spironolactone continued until end of follow-up	100 (41.2%)
Average duration of spironolactone use	304 days
Use of spironolactone discontinued before end of follow-up	143 (58.8%)
Average duration of spironolactone use	208 days
Spironolactone dose at first prescription	
25 mg	60 (24.7%)
50 mg	117 (48.2%)
100 mg	66 (27.2%)
Did not use an ACE-inhibitor at the start of spironolactone	86 (35.4%)
ACE-inhibitor use at start of spironolactone therapy	**(N=137)**
Started ACE-inhibitor simultaneously with spironolactone	11 (4.5%)
Continued ACE-inhibitor at the start of spironolactone	126 (51.9%)
Discontinued ACE-inhibitor at the start of spironolactone	20 (8.2%)
Continued use of ACE-inhibitors and spironolactone until end of follow-up	45/137 (32.8%)

and ACE-inhibitors was an inclusion criterion in RALES. It is therefore not surprising that this use is higher than in our study. Use of acetylsalicylic acid was lower in our population. However, a large proportion of our population were using oral anticoagulants. The relatively high use of oral anticoagulants can be attributed to the highly organised form of International Normalized Ration (INR) monitoring in the Netherlands. Striking is also the high use of potassium supplements in RALES. This could indicate some selection of patients with a tendency to hypokalemia in RALES.

With nearly 60% of patients discontinuing spironolactone, our data suggest that it is difficult to maintain patients on both drugs. In RALES only 214 (26%) patients discontinued spironolactone. A partial explanation for the higher discontinuation rate we find could be that patients in our population received higher average spironolactone dosages compared to RALES (55 mg vs. 26 mg), possibly resulting in more adverse effects.

Although our data do not provide the reasons for discontinuation, we suspect that patients in the general population doe not receive the same amount of monitoring and follow-up as patient in RALES. Close monitoring has been shown to be important in the management of heart failure patients [14,15]. Serum creatinine- and potassium monitoring is recommended for spironolactone users [16]. Emphasis on monitoring of patients with CHF is crucial, especially for the success of adding spironolactone to therapy in clinical practice. The fact that in daily practice a relatively older population seems to be exposed to these drug-combinations, makes monitoring even more important. Besides monitoring electrolytes and renal function, attention should also be given to other reasons for patients' discontinuations, such as perceived adverse reactions, patient attitudes to medication, lack of social support and treatment beliefs [17].

Conclusion

Currently there are three major classes of drugs available that have been shown to reduce morbidity and mortality in patients with CHF: ACE-inhibitors [18], betablockers [19] and spironolactone [1]. The use of these drugs in combination with a wide variety of medications necessitates close monitoring and an individual approach to patient therapy. Health professionals should be aware of this need for attention in CHF patients. Pharmacists might play a helpful role in this process [20]. Further research – at least in the Netherlands, is needed to monitor the actual use of these drugs in the general population with CHF.

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