Nephrol Dial Transplant (2022) 37: 407–408
https://doi.org/10.1093/ndt/gfab328
Advance Access publication date 2 December 2021

Spironolactone and chlorthalidone—old drugs, new uses—but approach with caution

Rajiv Agarwal

Division of Nephrology, Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, IN, USA

Correspondence to: Rajiv Agarwal; E-mail: ragarwal@iu.edu

Spironolactone was approved for the treatment of hypertension in 1960. In 1993, the Randomized Aldactone Evaluation Study (RALES) demonstrated that the use of this mineralocorticoid receptor antagonist reduced the risk of all-cause mortality by 35% among patients with severe heart failure with reduced ejection fraction [1]. A population-based time series surveillance study published 5 years later examined the trends in the rate of spironolactone prescriptions and the rate of hospitalization for hyperkalemia in ambulatory patients before and the publication of RALES [2]. The spironolactone prescription rate was 34 per 1000 patients in 1994 and it increased 4.4-fold immediately after the publication of RALES to 149 per 1000 patients by late 2001. The rate of hospitalization for hyperkalemia rose 4.6-fold, from 2.4 per 1000 patients in 1994 to 11.0 per 1000 patients in 2001. In part, this was because patients were being prescribed the drug when they had glomerular filtration rates (GFRs) lower than studied in the trial, but more importantly, in doses that were much higher than those used in the trial [3]. Despite firm indications for use, spironolactone use among patients with heart failure with reduced ejection fraction remains poor [4]. This story is familiar. The drug was inexpensive and access to the drug was not an issue. There was irrational exuberance for an inexpensive therapy. The harms were not recognized and it led to a therapy that was not embraced fully.

Chlorthalidone was approved by the US Food and Drug Administration (FDA) in 1960. In 2021, chlorthalidone was shown to be effective for the treatment of hypertension in patients with advanced chronic kidney disease (CKD) [5]. It is an inexpensive drug and there was an unmet need to treat hypertension in advanced CKD. There also appears to be irrational exuberance surrounding the publication. Can history repeat itself? I speculate that it will if we use it without careful attention to the adverse effects. The purpose of this editorial is to provide some guidance on how to use chlorthalidone sensibly in patients with advanced CKD and poorly controlled hypertension (Table 1).

The Chlorthalidone in Chronic Kidney Disease (CLICK) study demonstrated the drug is potent. For example, blood pressure lowering in the clinic at 4 weeks averaged 11.9 mmHg systolic [5]. The large drop in blood pressure, on top of 3.4 drugs, occurred rapidly and was associated with an approximate 10% decline in GFR. The dose of this drug was only 12.5 mg, or half the usual dose administered once daily. The blood pressure reduction was persistent. Many patients complained of dizziness, defined as feeling lightheaded when they stood up without a decrease in blood pressure >20 mmHg systolic. There were several patients who had asymptomatic hypokalemia, and reversible changes in serum creatinine were common.

Some lessons can be learned from the pilot trial that predated CLICK [6]. The pilot study showed that chlorthalidone 25 mg once daily produced a similar improvement in blood pressure at 4 weeks [6]. An even lower dose was used in the CLICK trial because it was felt that gradual lowering of blood pressure while the patients adjust to a newer lower volume state would improve the safety profile. Although chlorthalidone 12.5 mg daily was the starting dose in the CLICK trial [5], at 12 weeks the reduction in 24-h ambulatory systolic blood pressure was 10.5 mmHg, which was identical to that seen in the pilot study [6]. Therefore a starting dose of 12.5 mg was similarly effective as 25 mg of chlorthalidone. I speculate that an even lower dose of this drug might be safer.

In the CLICK trial, all patients were either on an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker or a beta-adrenergic blocker. These agents are known to enhance the response to diuretics. Furthermore, the response of chlorthalidone can be particularly great in patients who are on loop diuretics. Therefore, among patients with advanced CKD, particularly those on loop diuretics, I suggest that we initiate treatment with chlorthalidone at an even lower dose of 12.5 mg three times a week. Moreover, among patients on loop diuretics, the risk of reversible changes in creatinine was much higher than in patients who were not on these drugs

Table 1. Parallels between the two oldest antihypertensive drugs

Variable	Spironolactone	Chlorthalidone
FDA approval year	1960	1961
Year and name of clinical trial exploring a new use	1999, RALES	2021, CLICK
Target population	Symptomatic heart failure with reduced ejection fraction	Poorly controlled hypertension and stage 4 CKD
Study result	Reduced all-cause mortality, hospitalization for heart failure and symptoms of heart failure	Reduced 24-hour ambulatory systolic blood pressure at 12 weeks
Post-trial outcome	2004, increased frequency of hyperkalemia due to use in patients with low eGFR and higher doses of spironolactone compared to RALES	Likely to occur if clinicians are not careful with the use of this potent drug
Long-term outcome	Low prescription of evidence-based heart failure drug	To be seen

[6]. Therefore a lower dose of chlorthalidone (12.5 mg three times a week) might mitigate the risk of reversible changes in serum creatinine. Among patients not on loop diuretics, it would be reasonable to initiate treatment with chlorthalidone 12.5 mg administered once a day as was done in the CLICK trial.

In the CLICK trial, we invited patients 4 weeks after initiating or changing the dose of chlorthalidone to monitor blood pressure and kidney function. Dizziness was common; estimated GFR (eGFR) decreased, but this was reversible; and electrolyte disturbances such as a decrease in the levels of potassium, magnesium and sodium were observed. Increasing the chlorthalidone dose might provoke greater adverse effects with little change in blood pressure, as has been seen in the general population with hypertension [7]. Skeptics might argue that we should not use this drug because of the risk for acute kidney injury (AKI), but what we observed was a reversible decline in eGFR. Two weeks after stopping the study drug, eGFR returned to the baseline level. Furthermore, the long-term follow-up did not reveal a signal for an increased risk for kidney failure (defined as a persistent decrease in eGFR to <10 mL/min/1.73 m^2), kidney replacement therapy or death. In fact, the hazard ratio favored chlorthalidone [0.63 (95% confidence interval 0.36–1.13)]. Finally, randomized trials find a poor relation between the occurrence of reversible AKI and long-term kidney function [8].

In summary, chlorthalidone is potent, inexpensive and effectively reduces blood pressure among patients with advanced CKD. However, it has a potential to cause harm. Harms are manageable with periodic monitoring. It is not a drug to prescribe and forget (e.g. asking the patient to come back after 6 months). If we did so, it is quite likely that the patient might experience an adverse or serious adverse effect, an outcome that would replicate the history of spironolactone. Irrational exuberance is unwarranted.

FUNDING

R.A. is supported by the National Heart Lung and Blood Institute (grant R01 HL126903).

CONFLICT OF INTEREST STATEMENT

R.A. reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals, Akebia Therapeutics, Boehringer Ingelheim, Eli Lilly, Relypsa, Vifor Pharma, Lexicon and Reata; is a member of data safety monitoring committees for Vertex and Chinook and a member of steering committees of randomized trials for Akebia Therapeutics, Bayer and Reata; has served as an associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis and Transplantation* and has been an author for UpToDate; and has received research grants from the National Institutes of Health and the US Veterans Administration.

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: 709–717
2. Juurlink DN, Mamdani MM, Lee DS *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351: 543–551
3. McMurray JJ, O'Meara E. Treatment of heart failure with spironolactone—trial and tribulations. *N Engl J Med* 2004; 351: 526–528
4. Albert NM, Yancy CW, Liang L *et al.* Use of aldosterone antagonists in heart failure. *JAMA* 2009; 302: 1658–1665
5. Agarwal R, Sinha AD, Cramer AE *et al.* Chlorthalidone for hypertension in advanced chronic kidney disease. *N Engl J Med* 2021; doi: 10.1056/NEJMoa2110730
6. Agarwal R, Sinha AD, Pappas MK *et al.* Chlorthalidone for poorly controlled hypertension in chronic kidney disease: an interventional pilot study. *Am J Nephrol* 2014; 39: 171–182
7. Carlsen JE, Kober L, Torp-Pedersen C *et al.* Relation between dose of bendroflumethiazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 1990; 300: 975–978
8. Garg AX, Devereaux PJ, Yusuf S *et al.* Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA* 2014; 311: 2191–2198

Received: 13.11.2021; Editorial decision: 14.11.2021