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Monitoring of Renin-angiotensin-aldosterone-system (RAAS) Inhibitors and Diuretics Applied in General Hospital-Ikot Ekpene and St. Luke's Hospital-Uyo of Akwa Ibom State, Nigeria

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Authors' contributions

This work was carried out in collaboration between the authors. Author EUI designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Author JIL managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: Blockade of renin-angiotensin-aldosterone system (RAAS) has been shown to be beneficial in patients with hypertension, acute myocardial infarction, chronic heart failure and diabetic renal disease. However, RAAS inhibitors and diuretic therapy are associated with some side effects, notably electrolytes imbalance and renal impairment.
Objective: This study was aimed at assessing the extent of monitoring of renal function and electrolyte levels in cardiovascular disease patients managed with RAAS inhibitors and diuretics.
Methods: The study was carried out in two selected secondary health facilities (General Hospital-Ikot Ekpene and St Luke's Hospital-Uyo) in Akwa Ibom State, Nigeria between May and September 2016. The case notes of 600 (300 from each facility) cardiovascular disease patients managed with

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RAAS inhibitors and diuretics were retrieved from the hospital medical record of the study centers and reviewed. Relevant information was collected. Data obtained were analyzed using statistical program for social science (SPSS) version 17 with descriptive statistics.

Results: Of the 600 case notes studied, only 2.8% of the cases had a baseline monitoring of renal function and electrolyte concentrations. Only 2.2% of the cases had a follow-up monitoring (without baseline monitoring) of renal function and electrolyte concentrations. None of the cases studied had both baselines and followed up monitoring of renal function and electrolyte levels.

Conclusion: Non-adherence to guidelines on renal function and electrolytes monitoring was observed amongst the cases studied. The prescribers should be educated on the risks associated with lack of proper monitoring of renal function and electrolyte levels in cardiovascular disease patients managed with RAAS inhibitors and diuretics.

Keywords: Renin angiotensin aldosterone system; diuretics; electrolytes; monitoring.

1. INTRODUCTION

Monitoring in this context can be defined as the continual evaluation of biological samples (such as blood, urine, body tissue) for identification of health risks or in the course of therapy. [1]. Monitoring of drug treatment can have several effects such as improved adherence, better selection of drug therapy and better titration of treatment [2]. Monitoring can also, perhaps most importantly, identify potential adverse reactions to treatment.

Guidelines recommend that patients with newly diagnosed hypertension should have baseline biochemical tests of renal function and electrolytes concentrations before treatment with follow up monitoring at one week and four weeks after starting treatment and after that at intervals following any dose changes [3,4].

These recommendations are based on the supposition that pretreatment testing can discover rare secondary causes of hypertension and identify contraindications to treatment, and that post-treatment biochemical monitoring can identify changes related to adverse drug reactions (ADRs) before they cause serious or permanent effects, and so avert them [5].

A questionnaire survey suggested that general practitioners (GPs) often neglect biochemical monitoring [6].

Risk minimization through monitoring of renal function is recommended in clinical guidelines with subtle differences in timing, duration and frequency of monitoring as well as with changes in renal function that are considered acceptable.

Severe hyperkalemia, defined as serum potassium (K) level ≥6.0 mmol/L, can occur with all RAAS inhibitors especially in patients with renal insufficiency, diabetes or those taking potassium-sparing diuretics or potassium supplements. With patient education and close monitoring, hyperkalemia from RAAS inhibitors can be predicted and averted in many cases [7].

In clinical practice, renal function and potassium levels should be monitored similarly to the manner used in clinical trials. In general, a metabolic panel should be obtained within 72 hours of initiation, after 4 weeks of therapy and every 3–4 months routinely. After dose adjustments or pertinent changes in clinical status, laboratory monitoring of the serum creatinine and serum electrolytes should be carried out. Medication doses should be decreased for a serum potassium level >5.5 mmol/L and withheld for a serum potassium level >6.0 mmol/L. Since the initiation of angiotensin converting enzymes (ACEIs) and angiotensin II receptor blockers (ARBs) can be associated with an increase in serum creatinine, dose adjustment for the renal function should be individualized with intensification of monitoring in the setting of dynamic renal function changes. It is safe to avoid aldosterone antagonists with a potassium level ≥5.0 mEq/L or a serum creatinine level >2.5 mg/dl in men or creatinine level >2.0 mg/dl in women and to use them cautiously in patients with more modest renal insufficiency [8].

The appropriate prescribing and monitoring of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists, loop diuretics, thiazide diuretics, potassium-sparing diuretics, and aldosterone antagonists are important specifically in hypertension and chronic heart failure [9]. When initiating an ACEI or ARB according to Coleman *et al.,* it is important to measure baseline renal function and serum electrolytes as well as follow-up monitoring after initiation of the therapy [1].

Common risks associated with lack of proper baseline measurement and follow-up monitoring of renal function and serum electrolyte in patients receiving RAAS inhibitors and diuretics include hypotension, hyperkalemia, headache, dizziness, fatigue and renal impairment [3]. Renal impairment is a significant potential adverse effect of all RAAS inhibitors, therefore, renal function should be closely monitored.

Hyperkalemia is another possible complication associated with the use of RAAS inhibitors and diuretics due to their effect on aldosterone. As such, close monitoring of potassium level is required in patients receiving RAAS inhibitors and diuretics [3].

Several studies have shown that recommendations for biochemical monitoring are frequently not adhered to, sometimes resulting in serious adverse events [3]. A study of monitoring in patients receiving treatment for hypertension in primary care found that only 39% of patients taking ACEIs received baseline monitoring and many did not receive follow up monitoring [10]. The proportion receiving any form of monitoring was 38% [10]. This study is therefore aimed at assessing the extent of renal function and electrolytes level monitoring carried out in patients receiving RAAS inhibitors and diuretics in two selected secondary health care facilities in Akwa Ibom State, Nigeria.

2. RESEARCH METHODS

A cross-sectional drug utilization study was conducted using 600 randomly selected case notes of patients with cardiovascular disease placed on RAAS blockers and diuretics, obtained from the department of health information management of two selected secondary healthcare facilities in Akwa Ibom, Nigeria. The facilities selected for the study were General Hospital-Ikot Ekpene and St. Luke's Hospital-Uyo.

General Hospital-Ikot Ekpene is a government-owned secondary healthcare facility located at Ikot Ekpene Local Government, Akwa Ibom State, Nigeria. It was created in 1905 to cater for the healthcare needs of the nearby communities. It is now the major medical hub in the North Central Zone of Akwa Ibom State, Nigeria.

St Luke's Hospital-Uyo is a faith-based secondary healthcare facility established in 1937 by the Medical Missionaries of Mary from the Catholic Church.

Data were retrieved from the case notes of the patients seen in the selected study centres between May and September 2016. Sample size (n) was calculated according to the formula described by Yamane [11] as follows:

$$n = \frac{N}{1+N\,(e)^2}$$

where n = sample size, N = total number of cardiovascular disease patients managed with RAAS inhibitors and diuretics at the two facilities between the 8 weeks study period, e = precision level ($\pm$ 5.0%).

Although the calculated sample size was 407 case notes, 600 case notes (300 from each facility) were retrieved and reviewed. The patient case notes were returned as soon as the relevant information was collected. Information collected from each patient's case note was treated with utmost confidentiality.

The sampling frame for this study was the case notes of all cardiovascular disease patients of the selected hospitals who were managed with any of the following agents; angiotensin converting enzyme Inhibitors, angiotensin receptor blockers, aldosterone antagonists, direct rennin inhibitors, thiazides diuretics, and loop diuretics.

Quantitative data were analyzed using statistical program for social science (SPSS) version 17 computer package with descriptive statistics. Ethical clearance and formal approval for this study were obtained from the Akwa Ibom State Ministry of Health.

3. RESULTS

The pattern of use of RAAS inhibitors and diuretics, as well the extent of renal function and electrolyte monitoring in patients receiving these agents in the two hospitals used for the study is highlighted in Table 1.

In both hospitals studied, other anti-hypertensive agents co-prescribed with the RAAS inhibitors and/or diuretics were amlodipine [222(37%)], nifedipine [106(17.7%)], methyldopa [92(15.33%)], atenolol [32(5.3%)], propranolol [3(0.5%)] and metoprolol [2(0.3%)]. Most of the patients were also placed on non-antihypertensives. Among the prescribed drugs, the potentially harmful drug-drug interaction was noted in 29(4.8%) of the prescriptions while there

Table 1. Pattern of use of RAAS inhibitors and diuretics

Parameters	Frequency	Percentage (%)
ACEIs (n=338)		
Lisinopril	296	87.6
Ramipril	42	12.4
ARBs (n=177)		
Losartan	101	57.1
Telmisartan	71	40.1
Valsartan	5	2.8
Aldosterone antagonists (n=10)		
Spirinolactone	10	100
Diuretics (n=555)		
Hctz	495	89.2
Furosemide	43	7.7
Torsemide	17	3.1
Indication for use of RAAS blockers/diuretics (n=600)		
Hypertension	554	92.3
Congestive heart failure	42	7.0
Angina pectoris	4	0.7
Laboratory monitoring		
Baseline monitoring (n=600)		
Not carried out	583	97.2
Carried out	17	2.8
Follow up monitoring (n=600)		
Not carried out	587	97.8
Carried out	13	2.2

Hctz=Hydrochlorothiazide, ACEIs=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin II receptor blockers

was no potentially harmful drug-drug interaction in 571(95.2%) of the prescriptions. There was no documented side effect or adverse drug reaction to the RAAS inhibitors and diuretics prescribed. No contraindication to the use of any of the prescribed RAAS inhibitors/ diuretics was noted.

4. DISCUSSION

When initiating RAAS inhibitor and diuretic therapy it is Important to measure baseline renal function and serum electrolytes (National Institute for Health and Clinical Excellence [12]. Proper follow-up monitoring should be performed after initiation of the therapy.

The result of this study revealed the extent of renal function and electrolytes monitoring in cardiovascular disease patients receiving RAAS inhibitors and diuretics in two secondary health facilities in Akwa Ibom State.

ACEIs were the most commonly prescribed RAAS inhibitors followed by the ARBs. This agrees with the findings of a study conducted in a tertiary healthcare centre in North India [13]. However, a similar study reported by Bajaj in India found ARBs to be the most prescribed class of RAAS blockers [13]. ARBs are more expensive than the ACEIs. This may be the reason for the higher prescription rate of ACEIs than the ARBs as observed in our study. ACEIs have been shown to have a specifically beneficial effect on microvascular diseases of the kidney, by decreasing damage to both capillaries and arteries [14]. ACEIs are also effective in decreasing cardiovascular mortality and morbidity in patients with congestive heart failure and post-myocardial infarction [15,16].

Furthermore, we found that amongst the ACEIs, lisinopril was the most prescribed. Again, the relatively lower cost of this agent compared to other ACEIs may be responsible for the higher prescription rate of lisinopril.

Thiazide diuretics (89.2%) was the most frequently prescribed diuretic either as a monotherapy or combination therapy in the hospital's study. This agrees with the findings from previous studies in Britain, Italy, Spain, South Africa and Canada where thiazide diuretics has been shown to be the most popular medication for the treatment of hypertension [17,18,19]. This practice is in line with the JNC-8 report which has emphasized the use of thiazide

type diuretics as the first line agent for the management of hypertension [20]. Diuretics have been increasingly recognized as essential for blood pressure control due to their ability to reduce blood volume and cardiovascular resistance [21].

Baseline renal function and serum electrolytes monitoring were performed in only 2.8% cases studied. Furthermore, follow up monitoring was carried out several weeks after initiation of RAAS inhibitors and diuretics (without the initial baseline monitoring) in only 2.2% of the cases studied. No patient had both baselines and followed up monitoring of renal function and electrolyte concentrations in any of the study sites. This is quite worrisome. A similar study carried out by Professor Robin E. Ferner in United Kingdom found that 47% of 74,096 patients had baseline monitoring before the initiation of therapy and 36% had followed up monitoring. 18% had both baselines and followed up tests [1]. Our finding is consistent with the report of poor rates of renal function and electrolytes monitoring revealed in other studies [1]. An absence of baseline testing is inconsistent with standard guidelines. Hypertension guidelines have for more than 15 years stated that the measurement of serum electrolytes and urea or creatinine concentrations is essential. Simple baseline and follow up monitoring allow detection of some causes of secondary hypertension, associated cardio-vascular risk factors, evidence of target organ damage, and co-morbid diseases, all of which can influence treatment decisions [1]. An absence of monitoring makes changes in renal function and electrolyte concentrations more difficult to assess. Few patients had either baseline or follow up testing, while no patient had both baseline testing and subsequent monitoring, depriving the physicians of the opportunity to assess intra-individual renal function and electrolyte balance. ACEI/ ARB therapy is implicated in hyperkalemia of hospitalized patients and is considered a contributing cause in many of the hospitalized cases of hyperkalemia with some of the patients having serum potassium greater than or equal to 6 mmol/L [22,23,24] Despite widespread agreement that potassium monitoring is a component of good clinical care for patients prescribed ACEI/ARB, many patients placed on ACEI/ARB do not receive potassium and/or creatinine monitoring [25].

Renal function should be monitored in patients with hypertension receiving ACEI or ARB before initiating treatment, I week after starting treatment or any subsequent dose increase, at 4 and 10 days after starting treatment or increase in dose in patients at higher risk of developing hyperkalemia or deteriorating renal function (such as patients with peripheral vascular disease, diabetes mellitus, and older patients). This is because a major adverse effect of the ACEIs and ARBs is hyperkalemia or deterioration of renal function [26,27].

A limited elevation in serum creatinine (i.e. $\leq$ 30% above baseline) is a common occurrence in patients after the initiation of ACEI or ARB, and if it occurs, it will happen within the first 2 weeks of treatment [9].

Hypertensive patients with raised serum creatinine (>200umol/L) before staring treatment may have endovascular disease, intrinsic renal disease or obstructive uropathy, and therefore should be referred for specialist evaluation before receiving diuretic, ACEI or ARB treatment [10]. Referral is also commended if the serum creatinine rises above $\geq$ 30% and is associated with a large reduction in blood pressure after the initiation of treatment with ACEI or ARB, as this may suggest renovascular disease [16]. Patients with hypertension are often treated with ACEI or ARB, but many patients are also receiving other drugs. In many cases greater than three antihypertensive agents are needed to control blood pressure.

In hypertensive patients receiving thiazide or loop diuretics, electrolytes/renal function tests should be measured within 4 – 6 weeks of starting low dose thiazide diuretic treatment or loop diuretic treatment and thereafter, in all patients every 6–12 months, or if a person's clinical condition changes or a potentially interacting drug is added [26,28]. In patients receiving spironolactone or potassium – sparing diuretics, monitoring should be carried out before initiation of treatment (it should not be initiated if the potassium level is >5mmol/L), after 5 – 7 days with dose titration if required, every 5 – 7 days until the potassium values are stable, 1 – 2 times per year up to every 4 – 8 weeks during chronic treatment depending on risk factors (older patients, renal or cardiac dysfunction). Potassium – sparing diuretics should be withdrawn, and specialist advice sought if potassium rises to > 6mmol/L. Concomitant use of potassium sparing diuretics with ACEI or ARB should normally be reserved for practitioners experienced in such combinations and with

increased monitoring in high – risk patients [26,28].

5. CONCLUSION

The extent of monitoring of renal function and electrolytes levels in cardiovascular disease patients placed on RAAS inhibitors and diuretics is poor. There is a need to regularly remind our prescribers on the recommended guidelines related to the use of these agents. Furthermore, it is pertinent to emphasis this during the training of healthcare professionals in medical schools, pharmacy schools, and as well during the continuous professional development courses for physicians and pharmacists.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Coleman JJ, McDowell SE, Evans JW, Paramajit SG, Ferner RE. Oversight: A retrospective study of biochemical monitoring in patients beginning antihypertensive drug treatment in primary care. British Journal of Clinical Pharmacology. 2010;70:109-117.
2. Glasziou P, Irwig L, Mant D. Monitoring in chronic disease: A rational approach. British Medical Journal. 2005;3306:644-8.
3. Smellie WS, Forth J, Coleman JJ, Irvine W, Dore PC, Handley G, Williams DG, Galloway PJ, Kerr KG, Herriot R, Spickett GP, Reynolds TM. Best practice in primary care pathology: Review 6. Journal of Clinical Pathology. 2007;60:225-34.
4. Martin U, Coleman JJ. Monitoring renal function in hypertension: British Medical Journal. 2006;333:896-9.
5. Pirmohamed M, Ferner RE. Monitoring drug treatment. British Medical Journal. 2003;327:1179.
6. Kalra PA, Kumwenda M, MacDowell P, Roland MO. Questionnaire study and audit of use of angiotensin converting enzyme inhibitors and monitoring in general practice: The need for guidelines to prevent renal failure. British Medical Journal.1999;318:234-7.
7. Khosla N, Klaitzidis R, Bakris GL. Predictors of hyperkaelemia risk following hypertension control with aldosterone blockage. American Journal of Nephrology. 2009;30:418-24.
8. Hunt SA, Abraham WT, Chin MH. Focused update incorporated into the AA/AHA 2005 guidelines for diagnosis and management of heart failure in adults. 2009;119:e391-479.
9. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? Archives of International Medicine; 2000;160:685-693.
10. Anon. Lowering blood pressure in particular patient groups. Drug Therapeutics Bulletin. 2001;39:37-40.
11. Yamane T. Statistics: An introductory analysis, 2nd edition, New York: Harper and Row; 1967.
12. National Institute for Health and Clinical Excellence. Hypertension: Clinical management of primary hypertension in adults. NICE Clinical Guideline. 2011;127. Available:www.nice.org.uk/cg127
13. Bajaj JK, Sood M, Singh SJ, Jerath P. Prescription patterns of antihypertensive drugs and adherence to JNC VII guidelines in a tertiary care hospital in North India. International Journal of Medical and Clinical Research. 2012;3(2):118-120.
14. Bailey J, Grant P. The UK prospective diabetes study. The Lancet. 1998;352(9144):1932.
15. Pfeffer MA, Swedberg K, Granger CB. Effects of candesartan on morbidity and mortality in patients with chronic heart failure: the CHARM- Overall programme. Lancet. 2003;362:759-66.
16. Williams BN, Poulter M, Brown J. British hypertension society guidelines for hypertension management (BHS-IV):

summary. British Medical Journal. 2004; 328(7440):34-640.
17. Ford GA, Asghar MN. Management of hypertension in the elderly attitudes of general practitioners and hospital physicians. British Journal Clinical. Pharmacology. 1995;39(5):465-469.
18. Wallenius S, Kumpsala H, Parnanen TJ. Drug treatment for hypertension in Finnish primary health care. European Journal of Clinical Pharmacology. 1988;54:793-9.
19. Edward PR, Lunt DW, Fehrsen GS, Lombard CJ, Steyn K. Improving cost-effectiveness of hypertension management at a community health center, South Africa. South African Medical Journal. 1998; 88:549-54.
20. Evidence-Based Guideline for the Management of High Blood Pressure in Adults. Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8); 2014.
21. Suheela SH, Narendranth S, Somashekhar HS, Reshma SR, Keerthi SJ, Ramachandra K. Prescriptive pattern of antihypertensives in a tertiary care hospital using DU-90%. International Journal of Pharmaceutical Research and Development. 2011;4(1):107-113.
22. Ahuja TS, Freemn D Jr, Mahnken JD, Agraharkar M, Siddiqui M, Memon A. Predictors of the development of Hyperkalemia in Patients using angiotensin-converting enzyme inhibitors. American Journal of Nephrology. Africans: A review. World Journal of Cardiology. 2000;4:327-340.
23. Rastegar A, Soleimani M, Rastergar A. Hypokalaemia and hyperkalaemia. Postgraduate Medical Journal. 2001;77: 759-764.
24. Raebel MA, Ross C, Xu S. Diabetes and drug-associated hyperkalemia: Effect of serum potassium monitoring. Journal of General Internal Medicine. 2010;25:326-333.
25. McMurray J, Berry C. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone. American Journal of Medicine. 2001;111:587.
26. Scottish Intercollegiate Guideline Network. Hypertension in older people; 2001. Available:http://www.signac.uk/pdf/sign49pdf
[accessed on December 15, 2016].
27. Royal Infirmary of Edinburgh Renal Unit. How to start an ACEI.
Available:http://renux.dmed.ed.ac.uk/EdREN/Unitbits/ACEIstart.html
(accessed November 24, 2016).
28. Prodigy. Prodigyguidance: Hypertension.
Available:http//www.prodigy.nhs.uk/guidance.asp?2005
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