

RENAL FUNCTION AND ELECTROLYTE MONITORING IN CARDIOVASCULAR DISEASE PATIENTS RECEIVING RENIN-ANGIOTENSIN-ALDOSTERONE-SYSTEM (RAAS) INHIBITORS AND/OR DIURETICS.

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 is 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/or diuretics.

Method: 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 to September, 2016. The case notes of 300 cardiovascular disease patients managed with RAAS inhibitors and/or diuretics were retrieved from the hospital medical record in each of the study centres and reviewed and relevant information were collected. The data obtained was analyzed using statistical program for social science (SPSS) version 17 with descriptive statistics.

Results: Of the 300 case notes studied in each hospital, only 2% and 3.3% of the cases had a baseline monitoring of renal function and electrolyte concentrations in General Hospital-Ikot Ekpene and St Luke's Hospital-Uyo respectively. Only 2.3% and 2.0% had a follow up monitoring (without baseline monitoring) of renal function and electrolyte concentrations in General Hospital-Ikot Ekpene and St Luke's Hospital-Uyo respectively. None of the cases studied had both baseline and follow 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/or diuretics.

Key words: Renin Angiotensin Aldosterone system, Diuretics, Electrolytes, Monitoring.

Introduction

Monitoring is a process of checking a system that changes with time, so as to guide changes to the system that will maintain it or improve it [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 thereafter 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 of renal function that are considered acceptable.

Severe hyperkalemia, defined as a 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].

Progressive renal dysfunction can occur with Angiotensin converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) in the presence of hypovolemia or renovascular hypertension. Although this complication is more common in heart failure patients, and probably inherent to the pharmacological effect on renal hemodynamics, worsening renal function is usually mild and reversible. It is unfortunately one of the main reasons for the use of suboptimal doses.

In clinical practice, renal function and potassium levels should be monitored similar 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 obtained.

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 ACE-inhibitors and ARBs can be associated with an increase in serum creatinine, dose adjustment for 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 (ACEIs) and angiotensin receptor antagonists (ARBs), 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]. One recent 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.

RESEARCH METHOD

A cross sectional drug utilization study was conducted using 600 randomly selected case notes of patients with cardiovascular disease placed on RAAS blockers and/or 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 hospital established in 1937 by the Medical Missionaries of Mary, as an arm of the nunnery of the Catholic Church. The hospital has a 500-bed capacity. The Hospital was founded to help the mother and child. Beyond maternal healthcare, the hospital also is renowned for other medical services.

The study period for this work was between 1st May to 1st September, 2016 with eight weeks spent in each study centre. Sample size $\overline{(n)}$ was calculated according to the formula described by Yamane [11] as follows: $n = N / (1 + N(e)^2)$; where n = sample size, N = total number of cardiovascular disease patients managed with RAAS inhibitors and/or diuretics at the facility between the 8 weeks study period, e = precision level ($\pm 5.0\%$).

Although the calculated sample size for General Hospital-Ikot Ekpene and St Luke's Hospital-Uyo were 212 and 195 respectively, 300 case notes were retrieved and reviewed in each study centre. The patient case notes were returned as soon as the relevant information were 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 (ACEIs), Angiotensin Receptor Blockers (ARBs), Aldosterone antagonists, direct rennin inhibitors, thiazides diuretics, and loop diuretics.

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

RESULT

The pattern of use 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 below.

TABLE 1
PATTERN OF USE OF RAAS INHIBITORS AND DIURETICS

Parameters	GH-IK		SLH	
RAAS Blockers (n=254)	number	percentage	number	percentage
ACEIs	(n=180)		(n=158)	
<i>Lisinopril</i>	175	97.2	121	76.6
<i>Ramipril</i>	5	2.8	37	23.4
ARBs	(n=72)		(n=105)	
<i>Losartan</i>	36	50	65	62
<i>Telmisartan</i>	31	43.1	40	38
<i>Valsartan</i>	5	6.9	--	--
Aldosterone antagonists	(n=2)		(n=8)	
<i>Spirinolactone</i>	2	100	8	100
Diuretics	(n=277)		(n=78)	
<i>Hctz</i>	243	87.7	252	90.6
<i>Furosemide</i>	30	10.8	13	4.7
<i>Torsemide</i>	4	1.4	13	4.7
Indication for use of RAAS blockers/diuretics (n=300)				
<i>Hypertension</i>	275	91.7	280	93.3
<i>Congestive heart failure</i>	24	8.0	18	6.0
<i>Angina pectoris</i>	1	0.3	2	0.7
Laboratory Monitoring				
Baseline monitoring	(n=300)		(n=300)	
<i>Not carried out</i>	294	98.0	290	96.7
<i>Carried out</i>	7	2	10	3.3
Follow up monitoring	(n=300)		(n=300)	
<i>Not carried out</i>	293	97.7	294	98.0
<i>Carried out</i>	7	2.3	6	2.0

Hctz=Hydrochlorothiazide, ACEIs=Angiotensin converting enzyme inhibitors, ARBs=Angiotensin II receptor blockers, GH-IK=General hospital-Ikot Ekpene, SLH=St.Luke's hospital-Uyo.

In general hospital-Ikot Ekpene, other anti-hypertensive agents co-prescribed with the RAAS inhibitors and/or diuretics were amlodipine [117(39%)], nifedipine [41(13.7%)], methyldopa [48(16%)], atenolol [19(6.3%)] and metoprolol [2(0.7%)]. Most of the patients were also placed on non-antihypertensives. Among the prescribed drugs, potentially harmful drug-drug interaction was noted in 11(3.7%) of the prescriptions while there was no potentially harmful drug-drug interaction in 289(96.3%) 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.

In St. Luke's hospital-Uyo, other antihypertensives co-prescribed with RAAS inhibitors and/or diuretics were amlodipine [105(35%)], nifedipine [65(21.7%)], methyldopa 44(14.7%), atenolol [13(4.3%)], and propranolol [3(1.0%)]. As in General Hospital Ikot Ekpene, most of the patients in St Luke's Hospital-Uyo

[237(79%)] were also placed on non-antihypertensives. Furthermore, there was no documented side effect / adverse drug reaction to the RAAS inhibitors and diuretics prescribed. Also no contraindication to the use of the RAAS inhibitors / or diuretics was noted in St Luke's Hospital-Uyo. However, potentially harmful drug – drug interaction was identified in 18(6.0%) of the prescriptions while there was no potentially harmful drug-drug interaction noted in 282(94%) of the prescriptions.

DISCUSSION

When initiating RAAS inhibitor and/or 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/or diuretics in two secondary health facilities in Akwa Ibom State.

ACEIs were the most commonly prescribed RAAS inhibitors followed by the ARBs. This is in consonance 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 generally 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 in microvascular disease in 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 (81% in Ikot Ekpene and 83.9% in Uyo) was the most frequently prescribed diuretic either as a monotherapy or combination therapy in these study sites. This is in consonance 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 have placed emphasis on 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 was performed in only 2% and 3.3% of the cases studied in General Hospital-Ikot Ekpene and in St. Luke's Hospital-Uyo respectively. Furthermore, follow up monitoring was carried out several weeks after initiation of RAAS inhibitors and/or diuretics (without baseline monitoring) in only 2.3 and 2.0% of the cases in General Hospital-Ikot Ekpene and St Luke's Hospital-Uyo respectively. No patient had both baseline and follow 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 follow up monitoring. 18% had both baseline and follow up tests [1]. Our finding is consistent with the report of poor rates of renal function and electrolytes monitoring revealed in other studies [1]. Absence of baseline testing is inconsistent with standard guidelines. Hypertension guidelines have for more than 15 years stated that the measurement of serum electrolyte and urea or creatinine concentrations is essential. Simple baseline and follow up monitoring allow detection of some causes of secondary hypertension, associated cardiovascular risk factors, evidence of target organ damage, and co-morbid diseases, all of which can influence treatment decisions [1]. Absence of monitoring makes changes in renal function and electrolyte concentrations more difficult to assess. Few patients had baseline and follow up testing, 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, 1 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 ($>200\mu\text{mol/L}$) before starting 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 $>5\text{mmol/L}$), 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 $> 6\text{mmol/L}$. Concomitant use of potassium sparing diuretics with ACEI or ARB should normally be reserved for practitioners experienced in such combinations and with increased monitoring as for high – risk patients [26,28].

CONCLUSION

The extent of monitoring of renal function and electrolytes in cardiovascular disease patients placed on RAAS inhibitors and/or diuretics is poor. There is need to educate our prescribers on the recommended guidelines related to the use of these agents. This can be achieved by incorporating it in the curriculum of medical and pharmacy schools and also in the curriculum of the continuous professional development courses for physicians and pharmacists.

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