



ASSESSMENT OF ADVERSE DRUG REACTIONS OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) AMONG SUDANESE PATIENTS

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ARTICLE INFO

Article History:

Received 15th February, 2017

Received in revised form 10th March, 2017

Accepted 14th April, 2017

Published online 28th May, 2017

Key words:

Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARBs), Adverse Drug Reactions (ADR).

ABSTRACT

Introduction: Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are widely used in the treatment of hypertension, left ventricular dysfunction and diabetic nephropathy. Adverse effects of angiotensin II inhibitors include dry cough, dizziness, deterioration in renal function, hypotension and Angioedema.

Aim: This study aimed to evaluate the incidence of adverse drug reactions (ADR) of ACE inhibitors and angiotensin II receptor blockers among Sudanese patients.

Methodology: this was cross sectional study conducted in different hospitals and healthcare centers in Khartoum state, Sudan. A total of 120 patients were enrolled in this study. The data was collected using questionnaire.

Results: This study revealed that most of the patients (37.5 %) are using these drugs for less than one year, while 35 % of the patients used these drugs for 2 – 5 years and lisinopril was the most drug prescribed (78.3%) for the patients. About 75 % of the females did not receive advice regarding the use of these drugs during pregnancy. This study also showed that 46.7 % of patients developed first - dose hypotension and 36.7% of the patients suffered from dry cough.

Conclusion: Since 90.8% of the patients were not aware about the adverse drug reactions of their medications it is recommended to increase the awareness of the patients about the side effects of ACE inhibitors and ARBs.

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INTRODUCTION

The renin system is an important mediator of blood volume, arterial pressure, cardiac and vascular function. Components of this system can be identified in many tissues, but the primary site of renin release is the kidney. The renin system can be triggered by sympathetic stimulation, renal artery hypotension, and decreased sodium delivery to distal tubule⁽¹⁾. The system is activated when there is a loss of blood volume or a drop in blood pressure⁽²⁾.

Renin acts on oligopeptide substrate angiotensinogen to produce the decapeptide angiotensin I. In turn, angiotensin I is converted by angiotensin converting enzyme (ACE) to form octapeptide angiotensin II. Angiotensin II acts directly on the resistance vessels to: increase systemic vascular resistance and arterial pressure, stimulate the adrenal cortex to release aldosterone, which lead to increase cardiac and vascular hypertrophy^{(3) (4)}. The peptide angiotensin II (ANG II) plays an important role in cardiac and vascular disorder⁽³⁾.

Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are widely used in renal failure patients, in the treatment of hypertension, left ventricular dysfunction, and diabetic nephropathy⁽⁴⁾⁽⁵⁾. Their efficacy in these conditions is well established, and generally both classes of drugs are well tolerated, with a low incidence of site effect⁽¹⁾.

Adverse effects of angiotensin II inhibitors include cough, dizziness, and deterioration in renal function, although the overall incidence of hypotension and renal impairment in the consensus and solved studies was only 5%. Angioedema related to ACEIs is rare, although more common in patients of Afro-Caribbean origin than in other ethnic group⁽⁶⁾⁽⁷⁾.

Renin angiotensin inhibitors also demonstrate a less favorable response when used alone in black patient, although this is eliminated by addition of other drug. This reduce efficacy results from the low renin salt-sensitive profile and is particular propel in the elderly black patient^{(8) (9)}. Therapies aimed at modifying the renin system have been used extensively for treatment of hypertension, heart failure, myocardial infraction, and diabetes, and renal disease⁽¹⁰⁾.

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ACE inhibitors can be subdivided into 3 classes with regard to the active group the majority of ACE inhibitors are carboxyl-containing drugs (like lisinopril), a new class of ACE inhibitors possess a phosphoryl –group (like fosinopril) and sulfhydryl-containing drugs (like Captopril)⁽¹¹⁾.

ACEIs block conversion of angiotensin I to angiotensin II. Thus they inhibit angiotensin II release and bradykinin inactivation⁽¹²⁾.

Most ACE inhibitors are prodrugs which are converted by hepatic esterolysis to an active metabolite. The predominant elimination pathway of ACE inhibitors is excretion via the kidneys and for most ACE inhibitors, dosage adjustment is recommended in moderate and severe impairment of renal function⁽¹³⁾. The bioavailability among ACE inhibitors varies widely⁽¹⁴⁾.

On the other hand, angiotensin receptor blockers (also known as ARBs) are non-peptide compounds with varied structure⁽¹⁵⁾. ARBs selectively inhibit angiotensin II from activating the angiotensin-specific receptor (AT1) and they have no effect on bradykinin metabolism and therefore more selective blockers of angiotensin effect than ACEIs⁽¹⁶⁾. After oral administration, the ARBs are rapidly absorbed but they have a wide range of bioavailability⁽¹⁵⁾.

Angiotensin-converting enzyme (ACE) inhibitors have produced functional and clinical outcome benefits in clinical trials of patients with congestive heart failure, systolic dysfunction after myocardial infarction, and diabetic nephropathy. Similar favorable trends have been noted in observational studies in hypertension⁽¹⁷⁾⁽¹⁸⁾.

Black patients may be less sensitive than white patients to ACE inhibitors as monotherapy for hypertension, although ACE inhibitors are relatively ineffective as monotherapy in blacks⁽¹⁹⁾⁽²⁰⁾⁽²¹⁾.

Guidelines issued in 2009 by the European Society of Hypertension, and in 2011 by NICE (National Institute for Health and Clinical Excellence of Great Britain), recommend the use of an ACE inhibitor or angiotensin II receptor blocker (ARB) in younger and non-black patients⁽²²⁾.

It is reported that the combination of maximum doses of Aliskiren (direct renin inhibitor) and valsartan decreased blood pressure more than maximum doses of either agent alone but not more than would be expected with dual⁽²³⁾.

In patients with type I diabetes, blocking the RAS with angiotensin converting enzyme (ACE) inhibitors prevents progression from micro albuminuria to overt nephropathy, and in overt nephropathy decreases the gradual loss of renal function beyond its blood pressure lowering effect⁽²⁴⁾⁽²⁵⁾.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers are contraindicated in patients with bilateral renal artery stenosis due to risk of azotemia resulting from preferential efferent arteriolar vasodilator, vasodilation in the renal glomerulus due to inhibition of angiotensin II⁽²⁶⁾.

Therapy with ACEIs and ARBs is contraindicated in patients with a prior history of idiopathic Angioedema⁽²⁷⁾. Both ACE inhibitor and angiotensin receptor antagonist are contraindicated during pregnancy⁽²⁸⁾.

Angiotensin converting enzyme (ACE) inhibitors are useful first line drug in the therapy of mild and moderate hypertension. Adverse reactions to this drugs class are rarely serious. Hypotension, cough, rash, and taste disturbance are uncommon. Reduced glomerular filtration and hyperkalemia occur infrequently angioedema is rare and neutropenia is extremely rare⁽²⁹⁾.

In general, the ARBs are well tolerated. None of the drugs reviewed has a specific, dose-dependent adverse effect. The frequency of cough has been significantly lower in patients taking ARBs than in patients taking Lisinopril⁽³⁵⁾.

A well-documented side effect of ACEIs is a persistent dry cough, the frequency of which ranges from 5–20%. The side-effect usually develops within a few weeks after ACEIs initiation; is not dose-dependent and is more common in women. The persistent and troublesome nature of the cough often warrants discontinuation of the ACEIs, after which the side effect will usually abate within a few days. Substitution of the ACEIs with alternative agents, preferably angiotensin II antagonists, is recommended⁽³¹⁾⁽³²⁾.

ACE inhibitor-related angioedema is more common than was first imagined with the risk being as high as 5.54% in blacks. ACE inhibitor treated patients who have experienced an episode of angioedema can have a similar occurrence with angiotensin receptor blocker (ARB) therapy, albeit much less frequently. Angioedema, although life threatening, seldom proves fatal.⁽³³⁾

First dose hypotension has been recognized as a potential limiting factor in the use of ACE inhibitors in the treatment of chronic heart failure. Concerns regarding first-dose hypotension may increase the risk of renal, myocardial, or cerebral hypoperfusion. The incidence of first-dose hypotension after ACE inhibitors reported in large clinical trials is small, varying from 0.7% in the SAVE trial to 9.4% in the CCS-1 trial⁽³⁴⁾.

Hyperkalemia has been attributed to the use of ACE inhibitors in 10 to 38 percent of hospitalized patients with this complication. Hyperkalemia develops in approximately 10 percent of outpatients within a year after these drugs are prescribed. Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist⁽³⁵⁾.

Justification

Renin angiotensin aldosterone system inhibitor drugs such as ACEIs and ARBs are very useful in treatment of different diseases situation. However, most of the studies has been carried in countries other than Sudan. Taking in mind that there might be different factors such as genetic and diet among Sudanese which may affect their adverse drug reactions. Therefore, the aim of this study is to evaluate the safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers drugs in Sudanese patients.

METHODOLOGY

This was cross sectional study conducted in different hospitals and healthcare centers in Khartoum state, Sudan. It included Patients who are taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). A

total of 120 patients were enrolled in this study during May to September (2012), the data was collected using questionnaire.

Ethical consideration

This study was approved by the research committee of the faculty of pharmacy International University of Africa and also by the research committee, ministry of health Khartoum state, Sudan.

RESULTS

Table 1 Shows the distribution of gender in this study

Gender	Frequency	Percentage (%)
Male	63	52.5
Female	57	47.5
Total	120	100.0

Figure 1: Gender distribution

As shown in table (1) and figure (1), 52.5 % of the participants were males and 47.5 % were females.

Table 2 Shows the duration of treatment

Duration of treatment	Frequency	Percentage (%)
less than one year	45	37.5
Year	12	10.0
2-5 years	42	35.0
5-10 years	15	12.5
>10 years	6	5.0
Total	120	100.0

Figure 2: Shows the duration of treatment.

As shown in table (2) and figure (2) most of the patients (37.5 %) used the drugs for less than one year, while 35 % of the patients used the drugs for 2 – 5 years.

Table 3 Describe the Distribution of drugs used by the patients:

Drug	Frequency	Percentage (%)
candesartan	5	4.2
Captopril	2	1.7
Lisinopril	94	78.3
Losartan	17	14.2
Ramipril	1	0.8
Valsartan	1	0.8
Total	120	100.0

Figure 3: indicates the commonly used drugs.

It is found that Lisinopril was the most drug prescribed (78.3%) for the patients (table 3 and figure 3).

Table 4 Indicates the percentage of females who were advised to stop using drug during pregnancy and lactation period:

	Frequency	Percentage (%)
Yes	14	25
No	42	75
Total	56	100

Figure 4: describe the percentage of females who were advised to stop using the drugs.

This study revealed that 75 % of the females did not receive advice stop using these drugs during pregnancy and lactation period (table 4 and figure 4).

Table 5 shows the percentage of the patients who were aware about the adverse drug reactions of their medications:

	Frequency	Percentage (%)
Yes	11	9.2
No	109	90.8
Total	120	100

Figure 5: shows the awareness about adverse drug reactions. It is found that 90.8% of the patients are not aware about the adverse drug reactions of their medications (table 5 and figure 5).

Table 6 Frequency of Patient suffered from hypotension

First dose hypotension	frequency	Percentage (%)
Yes	56	46.7
No	64	53.3
Total	120	100

Figure 6: Indicates the frequency of the patients suffered from hypotension.

In this study 46.7 % of the patients suffered from hypotension (table 6 and figure 6).

Table 7 Frequency of patients suffered from cough

	Frequency	Percentage (%)
Yes	44	36.7
No	75	62.5
Total	119	99.2
Missing	1	0.8
Total	120	100.0

Figure 7: Describe the percentage of the patients suffered from cough

As in table (7) and figure (7), 36.7% of the patients suffered from dry cough.

Table 8 Number of patients who measured serum potassium level

Measured serum potassium level	Frequency	Percentage (%)
Yes	23	19.2
No	97	80.8
Total	120	100

Figure 8: Shows the number of patients who measured serum potassium level.

Table (8) and figure (8) shows that 80.8 % of patient did not measure their serum potassium level.

Table 9 Number of patients with hyperkalemia

Serum potassium level	Frequency	Percentage (%)
Hyperkalemia	9	39.1
Normal	14	60.9
Total	23	100

Figure 9: Indicates the number of patients developed hyperkalemia.

This study indicated that 39.1% of the patients who measured their serum potassium level suffered from hyperkalemia (table 9 & figure 9).

DISCUSSION

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers are widely used in the treatment of hypertension, left ventricular dysfunction, and diabetic nephropathy ⁽⁴⁾⁽⁵⁾. Adverse effects of angiotensin II inhibitors include cough, dizziness, and deterioration in renal function. Angioedema related to ACEIs is rare, although more common in patients of Afro-Caribbean origin than in other ethnic group ⁽⁶⁾⁽⁷⁾.

This research was conducted to evaluate the incidence and awareness of adverse drug reactions of angiotensin converting

enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in Sudanese patients.

In this study 52.5% of the study population were male and 47.5% were female. The duration of the treatment for the majority of the patients (37.5 %) is less than one year.

Generally, different drugs of ACEIs and ARBs are regularly used among the population, but the most common drug is Lisinopril (78.3 %), factors considered may be due to its wide distribution, availability and affordable cost.

This study showed poor awareness about the use of renin system inhibitors during pregnancy about 75 % of the females in this study indicated that they did not receive advice to stop using these drugs during pregnancy and lactation. Myla et al. (2012) stated that ACEIs and ARBs, are strictly prohibited in pregnancy due to their undesirable effects on the fetus⁽²⁸⁾.

As indicated this study focused on the side effects of ACEIs and ARBs. 90.8 % of the patients included in this study were not aware about the adverse drug reactions of renin system inhibitors.

This research revealed that 46.7% of patients suffered from first dose hypotension. This percentage is considered high compared to other studies which reported that the incidence of first-dose hypotension after ACE inhibitors reported in large clinical trials is small, varying from 0.7% in the SAVE trial to 9.4% in the CCS-1 trial⁽³⁴⁾.

36.7 % of the patients suffered from the dry cough. It is reported that the frequency of dry cough ranges from 5–20% and usually develops within a few weeks after ACEIs initiation; is not dose-dependent and is more common in women. The persistent and troublesome nature of the cough often warrants discontinuation of the ACEIs, after which the side effect will usually abate within a few days⁽³¹⁾⁽³²⁾.

80.8% of the patients were not asked to measure their serum potassium level.

This study showed that 39.1 % of the patients who measured serum potassium level developed hyperkalemia. It is reported that hyperkalemia has been attributed to the use of ACE inhibitors in 10 to 38 percent of hospitalized patients with this complication and hyperkalemia develops in approximately 10 percent of outpatients within a year after these drugs are prescribed. Patients at greatest risk for hyperkalemia include those with diabetes and those with impaired renal function in whom a defect in the excretion of renal potassium may already exist⁽³⁵⁾.

CONCLUSION

This study showed poor awareness about the use of renin system inhibitors during pregnancy and the incidence of first dose hypotension and dry cough is high. Therefore, awareness about the use, side effects and drug-drug interactions of Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers should be improved.

Acknowledgement

This work was supported by the faculty of Pharmacy, International University of Africa, Sudan.

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