INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

# A RETROSPECTIVE STUDY ON THE POTENTIAL DRUG INTERACTION BETWEEN ANGIOTENSIN CONVERTING ENZYME INHIBITOR OR ANGIOTENSIN RECEPTOR ANTAGONIST AND OTHER DRUGS IN END-STAGE CHRONIC RENAL FAILURE PATIENTS

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Article Received on: 13/08/12 Revised on: 20/09/12 Approved for publication: 12/10/12

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**ABSTRACT**

Increasing number of chronic renal failure (CRF) patients had reflected an increase in the number of patients with diabetes and hypertension. Therefore, health practitioners would be faced with management of complicated medical problems for the patients of chronic renal disease. In this way, various complications of chronic renal failure would lead to polypharmacy, where the patients receive three to five drugs in a dose. Development of polypharmacy had made the potential of drug interaction greater. The objective was to determine whether CRF patients admitted to hospital with specific adverse drug reactions were likely to have been prescribed with interacting drugs. Retrospective study was designed. The study was conducted at the General Practice Rooms Floor 1 – Floor VI of Central Army Hospital Gatot Soebroto Jakarta. The study was conducted from December 2011 – February 2012. The data were collected in a retrospective way for a year (January – December 2011). End-stage CRF patients who were having hemodialysis therapy and receiving ACE Inhibitor drugs or Angiotensin II Receptor Antagonist (AIIRA) and receiving treatment at the General Practice Rooms at Central Army Hospital Gatot Soebroto Jakarta. During the period of January – December 2011, 84 patients were treated with end-stage CRF at the Central Army Hospital and having routine hemodialysis and 44 patients were receiving therapy with ACE Inhibitor and AIIRA. Other drugs simultaneously given with ACE Inhibitor and AIIRA were captopril-spironolactone, captopril-aspirin, captopril-allopurinol, captopril-KSR, captopril-furosemide, lisinopril-furosemide and valsartan-mefenemic acid. An increase in adverse effects of the drugs was found based on the clinical evaluation and laboratory examination. The adverse effects included hyperkalemia (9,09%), decrease in anti-hypertension effect (6,8%), acute hypotension (40%), and declining renal function (11,36%). The study identifies drug interaction in end-stage CRF patients who received ACE Inhibitor or AIIRA. This study highlights the need for screening prescriptions of for pDDIs and proactive monitoring of patients who have identified risk factors; this helps in detection and prevention of possible adverse drug interactions.

**Keywords**: ACE Inhibitor drugs, Angiotensin II Receptor Antagonist, hemodialysis, hyperkalemia

## INTRODUCTION

Chronic renal failure is a progressive and irreversible renal function disorders, in which the body fails to maintain its metabolism and liquid and electrolyte balance. Chronic renal failure is a global public health problem. According to United State Renal Data System (USRDS), prevalence of chronic renal failure (CRF) increased by 20-25% every year in the United States. [1] In Canada, the average incidence of end-stage renal failure was 6,5% every year (Canadian Institute for Health Information (CIHI), 2005), with an average increase in prevalence of 69,7% since 1997 (CIHI, 2008). [2] In Indonesia, no complete data had been available on the prevalence of renal failure, including the number of chronic renal failure patients. It was estimated that the number of renal failure patients kept increasing in Indonesia. WHO estimated that there would be a 41,4% increase in the number of renal failure patients in Indonesia.

Chronic renal failure (CRF) cases were always related to hypertension. In the United States, for instance, about 30% of end-stage renal failure cases were found to have a relationship with hypertension. [3] Treatment of hypertension in CRF patients is useful to reduce blood pressure in addition to preventing the damage of target organs. Selection of anti-hypertensive drugs for CRF patients was based upon other beneficial effects besides anti-hypertensive effects, for instance, their ability to reduce proteinuria and their nephroprotective and cardioprotective properties. The main anti-hypertensive drugs used for CRF patients were Angiotensin-Converting Enzyme (ACE) Inhibitor (such as captopril, lisinopril) and Angiotensin II Receptor Antagonist (AIIRA) (such as valsartan, cadesartan). ACE Inhibitor and AIIRA were recommended since they had nephroprotective properties. [4,5]

The increasing number of CRF patients reflects an increase in the number of patients with diabetes and hypertension. Therefore, health practitioners would be faced with management of complicated medical problems for the patients of chronic renal disease. [6] In this way, various complications of chronic renal failure would lead to polypharmacy, where the patients receive three to five drugs in a dose. Development of polypharmacy had made the potential of drug interaction greater.

The study found that a total of 474 potential drug interactions were identified, and the number of drug interactions were found to increase relatively with the increase in hospitalization days and number of drugs given per prescription (polypharmacy). Most of the drug interactions were of delayed onset, moderate severity, level II significance and predominantly due to cardiovascular and antimicrobial drugs. The study emphasizes that the surveillance and presence of a clinical pharmacist is important in a hospital setting. [7]

Based on the description above, a respective study is needed to find out potential drug interaction between Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Antagonist with other drugs in end-stage chronic renal failure patients at Inpatient Room of Central Army Hospital Gatot Soebroto Jakarta.

## METHOD

A retrospective study was carried out for a period of 12 months (between January 2011 and December 2011).

Population of the study was all end-stage Chronic Renal Failure (CRF) patients who were having hemodialysis therapy, receiving ACE Inhibitor or Angiotensin II Receptor Antagonist (AIIRA), and treated at Inpatient Rooms of Central Army Hospital Gatot Soebroto Jakarta. The samples were taken with *Krejcie Morgan* sampling technique. [8]

Formula of *Krejcie Morgan* sampling*;*

$$n = \frac{x^2 . N . P(1-P)}{(N-1).d^2 + x^2 . P(1-P)}$$

Description

n = number of samples
N = number of population
$X^2$ = chi-square value
P = proportion of population
D = estimation of error

Data of samples that had been selected using *Krejcie-Morgan* formula were based upon the following inclusion and exclusion criteria:

**Inclusion criteria**

1. End-stage chronic renal failure (CRF) patients who were having routine hemodialysis
2. Secondary hypertensive patients with consistent systolic and diastolic blood pressure > 90mmHg and >140 mmHg, respectively
3. CRF patients who received antihypertensive drugs of Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin II Receptor Antagonist (AIIRA)
4. In-patient CRF patients who stayed at the General Practice Room of Central Army Hospital Gatot Soebroto Jakarta
5. Using anti-hypertensive drugs of ACE Inhibitor and/or Angiotensin II Receptor Antagonist (AIIRA) for more than 4 weeks
6. End-stage CRF patients with anemia, acidosis, and renal osteodystrophy
7. End-stage chronic renal failure (CRF) patients with hypertension, diabetes mellitus, lung TB, and congestive heart failure

**Exclusion criteria**

1. Pregnant and/or breastfeeding women
2. Female patients who used contraceptives
3. Un-hospitalized patients at the Central Army Hospital Gatot Soebroto Jakarta
4. Cancer patients

Ethical approval was obtained from the relevant Institutional ethics committee prior to study initiation. Prescriptions with two or more drugs prescribed were selected for the study. Prescriptions from each patient during his/her hospitalization in the ward during the study were included. Demographic information (age and sex), length of hospital stay, main diagnosis and details of co-morbidities were obtained from the clinical records.

**Data Collection**

Retrospective data that had been collected were analyzed in a descriptive way to find out the adverse effect of potential drug interaction between ACE Inhibitor and AIIRA in Chronic Renal Failure (CRF) patients. The data were analyzed based on the objective of the study, namely, to determine percent incidence of each adverse effect due to the potential drug interaction of anti-hypertensive agents that acted on the Renin-Angiotensin-Aldosterone System (RAAS) at the General Practice Rooms of Central Army Hospital Gatot Soebroto Jakarta.

**Table 1: Demographic characteristics and primary admission diagnosis of total patients admitted to the CCU**

| Characteristic | Value |
|---|---|
| **Gender** | |
| Male | 31 – 70,5% |
| Female | 13 – 29,5% |
| **Age (years)** | |
| Mean ± SD | 51,5 ± 10,07 |
| Minimum-maximum | 41 – 74 |
| **Stay duration (days)** | |
| Mean± SD | 5,31 ± 1,9 |
| Minimum-maximum | 3 – 10 |
| **Primary admission diagnosis** | |
| Chronic kidney disease | 72,72% |
| Nephrolithiasis | 4,54% |
| Uremic gastropathy | 4,54% |
| Hypertensive Heart Disease | 4,54% |
| uremic encephalopathy | 2,27% |
| Haematuria | 2,27% |
| Diabetic nephropathy | 2,27% |
| Diabetes Mellitus | 2,27% |
| Pulmonary Oedema | 2,27% |
| Stroke | 2,27% |

**Table 2: Potential Drug Interaction of ACE Inhibitor**

| ACE Inhibitor | Other drugs | Severity level | Effect |
|---|---|---|---|
| Captopril | | | Cough, Declining renal function |
| Captopril | Spironolactone | Major - Probable | Hiperkalemia (Drug Interactions Facts) |
| Captopril | Aspirin | Moderate - Possible | Hypotension, Reduction of captopril vasodilator effect (Drug Interactions Facts) |
| Captopril | Allopurinol | Major - Possible | Increasing the risk of hypersensitive reaction (Drug Interactions Facts) |
| Captopril | KSR | Moderate - Possible | Hiperkalemia (Drug Interactions Facts) |
| Captopril | Furosemide | Minor – Suspected | Acute hypotension, Reducing effect of furosemide (Drug Interactions Facts) |
| Lisinopril | Furosemide | Moderate - | Acute hypotension |
| Valsartan | Mefenamic acid | Moderate - Probable | Reduction of captopril vasodilator effect (Drug Interactions Facts) |

**Table 3: Results of laboratory tests involved by ACE Inhibitor-AIIRA drugs adverse reaction**

| Results of Laboratory Test | n (%) |
|---|---|
| Haemoglobin | 97,7% |
| Haematocrit | 97,7% |
| Erythrocyte | 79,5% |
| Leukocyte | 6,81% |
| Thrombocyte | 4,54% |
| Ureum | 100% |
| Creatinine | 100% |
| Natrium | 2,27% |
| Kalium | 22,72% |
| Chloride | 2,27% |
| Urine Protein | 2,27% |

N(%) -> Percent patient with abnormal finding

**Table 4: Clinical manifestations, frequency, sex ratio and ACE Inhibitor-AIIRA drugs suspected of causing adverse reactions**

| Type of ADR | n(%) | male/female | suspected drug (n) |
|---|---|---|---|
| Dizziness | 2,27 | Female 2,27% | Captopril |
| cough | 11,36 | Male 9,09%<br>Female 2,27% | Captopril |
| fatigue | 29,54 | Male 11,35%<br>Female 18,8% | Valsartan |
| vomit | 20,45 | Male 13,64%<br>Female 6,81% | |

## RESULTS AND DISCUSSION

Of the total 239 CRF patients, 84 patients were having routine hemodialysis (end-stage CRF). Of the 84 end-stage CRF patients, only 50 end-stage CRF patients were receiving ACE Inhibitor or AIIRA. Using *Krecjie Morgan* formula for a population (N) = 50, 44 patients were selected as samples. Most of samples were male (data presented in Table 1). This is consistent with a meta-analysis study, suggesting that men were potential to have renal diseases than women were. Correlation with hormonal influence had been uncertain since no information had been available on the influence of estrogen and progesterone hormones with the progressivity of renal damage. However, an animal experiment had shown a renoprotective property of both hormones on the renal mesangial cells[9] and lasted for 31 to 60 years. An analysis conducted by NHANES III (National Health and Nutrition Examination Survey) revealed that prevalence of CRF was increasing with age, black race, male gender, and hypertension. [10] Table 1 also indicates that mean hospital stay was 3-10 days, and main diagnoses were chronic kidney disease (72,72%), uremic gastropathy (4,54%), hypertensive heart disease (4,54%), uremic encephalopathy, haematuria, diabetes mellitus nephropathy, diabetes mellitus, pulmonary oedema, and stoke (2,27%, respectively).

Data of potentially interacting drugs given to te patients are presented in Table 2. Table 2 indicates that in 44 end-stage CRF patients who were treated and having routine hemodialysis at the Central Army Hospital Gatot Soebroto Jakarta, drug interaction was found in 4 patients (9,09%). Drug interaction occurred in the patients receiving captoril or valsartan combined with Spironolactone or KSR. Measurement data shows that mean serum kalium was 6,1 mEq/L above the normal serum kalium of 3,5 – 5,3 mEq/L (laboratory data presented in Table 3). Reardon and Macpherson (1998) suggested that prevalence of hyperkalemia during a period of two years was 11%.[11,12] Nonetheless, a previous study found that about 20,5% of hyperkalemic patients had potential drug interaction. [13] A study conducted by Egger et al (2003) reported that due to the combined effect of ACE Inhibitor and kalium-effective diuretics, the prevalence of hyperkalemia was 5,2%, while the study found a prevalence of 9,09%.[14] Three (6,8%) of 44 the end-stage CRF patients had drug interaction, namely, reduction of anti-hypertensive effects. Drug interaction occurred between ACE Inhibitor and AINS. Hansten and Horn (2001) suggested that combined use of aspirin and ACE Inhibitor caused a reduction in ACE Inhibitor effect in renal failure patients, but the interaction was weaker with low-dose aspirin. Aspirin inhibitory effect depended upon the dose. [15] The study found that 19 of 44 patients received aspirin combined with ACE Inhibitor or AIIRA, but reduction of anti-hypertensive effects was not significant in the patients since the dose of aspirin mostly used for the patients was 80 mg/day. Forty percent of the patients received furosemide combined with ACE Inhibitor or AIIRA. However, adverse effect in the form of acute hypotension was not found since the adverse effect usually occurred at the initial use of ACE Inhibitor or AIIRA combined with diuretics, while the study used the final data of the patients. Five (11,36%) of the 44 patients had a declining renal function due to the therapy with ACE Inhibitor or AIIRA.

## CONCLUSION

The retrospective study on the potential drug interaction of ACE Inhibitor and AIIRA with other drugs used for end-stage CRF patients concludes the following points.

1. The study shows that not all patients who received combined captopril and spironolactone had drug interaction;
2. Cough is one of captopril side effects. Three (6,8%) of 44 end-stage CRF patients receiving ACE Inhibitor had cough as an adverse effect. According to K/DOQI, female patients usually had cough as an adverse effect, but according to the observation in this study, male patients had cough as an adverse effect;
3. The study still found combined used of Allopurinol and captopril, which were reported to cause *Steven Johnson syndrome*, hypersensitive reaction, increase in leukopenic reaction, and serious infections. Therefore, combined use of allopurinol and captopril must be avoided, particularly for renal failure patients. It is necessary to take a tight control upon hypersensitive signs (such as skin reaction) or low leukocyte (lesion on larynx, fever), particularly in renal failure patients. Leukocyte monitoring before use and periodic monitoring every 2 weeks were important during the first 3 months of treatment.
4. ACE Inhibitor and AIIRA were said to reduce proteinuria in CRF. A controlled experiment on chronic renal failure even found that ACE Inhibitor and AIIRA reduced protein excretion about 30% - 40% greater than other anti-hypertensive agents did. However, this study found only 1 of 44 patients had proteinuria as an adverse effect.

## ACKNOWLEDGMENT

Dr. Komarudin Boenjamin, SpB. Head of Central Army Hospital (RSPAD), Jakarta, Indonesia

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Source of support: Nil, Conflict of interest: None Declared