Adverse Drug Reactions Among End-Stage Renal Failure Patients ec Diabetes Mellitus In General Hospital Pulau Pinang-Malaysia

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ABSTRACT

Our study aimed at evaluating Adverse Drug Reactions (ADRs) among chronic kidney disease patients of the End-Stage Renal Failure (ESRF) secondary to Diabetes Mellitus. Retrospective cross-sectional study was used as the method of this study..Naranjo Scale was used to observe ADRs among patients. Statistical analysis was done using statistical package of social sciences (SPSS 17®). Ethical clearance was done with respective clinical research committee. Study findings showed that from 200 patients, 5.5% have probable, 15% possible and 79.5% doubtful ADRs. Hypoglycemia (2.5%) had the highest number of probable ADR. Insulin (1.5%) and gliclazid (1%) were the major cause of probable ADRs. Analysis showed significant correlation (*sig.<0.05*) between age and ESRF secondary to diabetes mellitus. Patient with ESRF secondary to diabetes mellitus above 55 years are tend to have ADRs. Analysis also showed that no significant correlation (*sig.>0.05*) between adverse drug reactions and ESRF patients secondary to diabetes mellitus.

Keywords: Adverse drug reactions, end-stage renal failure, diabetes mellitus, naranjo scale.

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Introduction

Diabetes mellitus is a group of metabolic disorders that results in defection of insulin secretion, insulin sensitivity, or both. Diabetes mellitus, especially type 2 diabetes, is a public health concern, nowadays are alarming. Diabetes mellitus is the most frequent cause of chronic kidney disease worldwide. Diabetes affects over 170 million people worldwide, and this will rise to 300 million people by 2025 (WHO,2002). Over the past 2 decades, we can see there has been a continuous increase in the incidence of end-stage renal disease (ESRD) due to diabetes, predominantly in those with type 2 diabetes.

Under normal conditions each of the two million nephrons of the kidney work in an organized approach to filter, reabsorb, and excrete various solutes and water. The kidney is a primary regulator of sodium and water as well as acid-base homeostasis. The kidney also produces hormones necessary for red blood cell synthesis and calcium homeostasis. Impairment of normal kidney function is often referred to as renal insufficiency.

Chronic kidney disease (CKD), is defined as a progressive loss of function occurring over several months to years, and is char acterized by the gradual replacement of normal kidney architecture with interstitial fibrosis. CKD is further categorized by the level of kid ney function (as defined by GFR) into stages 1 through 5. it is necessary to denote at this point that Stage 5 was previously referred to as end-stage renal disease (ESRD).

Adverse Drug Reaction (ADR) according to WHO,1972 is unwanted condition because of the drugs that appear in prophylaxis, diagnosis, and therapeutic dose. ADR is estimated occur almost in 20% drugs consuming. This condition could raise twice in the hospital. (WHO, 2010). Some of methods that the authority use to determine ADR are *Naranjo scale* and WHO *assessment scale* . To determine preventability of ADR the authority use *Schumock* dan *Thornton scale*. (Palaian S, *et al*, 2006).

WHO suggest for every health profession must inform the ADR happens to prevent patient suffering and decrease medicinal fee because of the ADRs.

Pharmacist as one of health professional should be able to identify ADR, understand influence of drug to disease, influence of disease to drug pharmacokinetics. These are done to determine that drug is given precise and minimalize ADR and toxicity. Pharmacist should be understood the changes in laboratory values to evaluate clinical condition. In this research we monitor all the ADRs that will happen in

patients with Diabetes Mellitus complicated by Chronic Kidney Disease. These patients of course not receive one drug but two or more drugs. In these case presence of ADRs may increase.

Methodology

Research was held in General Hospital Pulau Pinang Malaysia from January 2011 untill April 2011. This research contains retrospective design, with convenience sampling. Every Diabetes Mellitus with Chronic Kidney Disease patient during 2010 was concluded to this research. Inclusion criteria were End-Stage Renal Failure patient and a-20 until 60 years old patients. This research is licensed under Clinical Research Centre (CRC) Pulau Pinang Malaysia. While the exclusion criteria were Diabetic mellitus type I patients, patients with endocrine disorders (e.g., acromegaly, Cushing's syndrome), and patients with diseases of the exocrine pancreas (e.g., pancreatitis). Data analyse was processed using SPSS 17 (Statistical Package of Social Sciences).

Result and Discussion

There are 1000 population of End-Stage Renal Failure patient during 2010. 200 of them are used as sample size using raosoft equation and convenient sampling. Which are:

N (sample size) = 200
Margin error = 6,20%
Confidence level = 97,8%

There are two major comorbidity in end-stage renal failure cases, they are diabetes mellitus and hypertension, these are called initiation factor. Initiation factors include diabetes mellitus, hypertension, autoimmune disease, polycystic kidney disease, and drug toxicity (Joy, et al., 2008).

The first clinical sign of renal disfunction in diabetic patients is microalbuminuria, microalbuminuria progress to macroalbuminuria or overt proteinuria. Patients with proteinuria developed chronic kidney disease which ultimately requires dialysis or transplantation (Ruggenenti & Remuzzi, 2009).

Table 1 shows at the onset of diabetes the glomerular filtration rate (GFR) may be elevated, and there are no evident clinical abnormalities (stage I diabetic nephropathy). Then, with good metabolic control the GFR normalizes (stage II), and over about 10 years microalbuminuria may develop (stage III or incipient nephropathy). Then, albuminuria may increase to the macroalbuminuric range and theGFRstarts to decline (stage IV, or overt nephropathy) until kidney failure develops (stage V). More recent evidence, however, suggests that diabetic kidney disease is a continuum. It starts with the appearance of measurable amounts of albumin in the urine and evolves, with a progressive increase in albumin excretion, to a progressive decline in GFR.Not only is this associated with an increased urinary excretion, but also of other plasma components and, without specific treatment, may eventually result in terminal kidney failure.

Table 1. Stages of Diabetic Nephropathy

Stage	Years diabetes on set	GFR	UAE (g/min)	Findings
I Hyper-perfusion	0	Elevated	>20	Enlarged kidneys
II Clinical Latency	10–15	Normal-elevated	<20	High-normal BP
III Incipient Nephropathy	15–20	Normal-elevated	20–200	Hypertension
IV Overt Nephropathy	20–30	Reduced/decreasing	>200	Worsening hypertension
V Kidney Failure	>30	Severely reduced	>200	Severe hypertension

Hypertension is also a consequence of renal disease. Reduction in nephron number of any cause, intrarenal inflammation, and increased intrarenal angiotensin II and oxidative stress result in a tendency to sodium retention, leading to hypertension (Rodriguez-Iturbe & Villalobos, 2009). Hypertension is closely linked with the kidney—the kidney may have a role in the pathogenesis of hypertension and it may also be a prime target of damage caused by hypertension**.** Both renal parenchymal disorders and renovascular disorders may be associated with hypertension (Sweetman, 2007). The Renin Angiotensin Aldosteron System (RAAS) regulates sodium, potassium, and fluid balance. Therefore, this system significantly influences vascular tone and sympathetic nervous system activity and is the most influential contributor to the homeostatic regulation of BP. Renin is an enzyme that is stored in the juxtaglomerular cells, which are located in the afferent arterioles of the kidney.

The release of renin is modulated by several factors: intrarenal factors (e.g., renal perfusion pressure, catecholamines, and angiotensin II) and extrarenal factors (e.g., sodium, chloride, and potassium). Juxtaglomerular cells function as a baroreceptor-sensing device. Decreased renal artery pressure and kidney blood flow are sensed by these cells and stimulate secretion of renin. The juxtaglomerular apparatus also includes a group of specialized distal tubule cells referred to collectively as the macula densa. A decrease in sodium and chloride delivered to the distal tubule stimulates renin release. Catecholamines increase renin release probably by directly stimulating sympathetic nerves on the afferent arterioles that, in turn, activate the juxtaglomerular cells. Decreased serum potassium and/or intracellular

calcium is detected by the juxtaglomerular cells, resulting in renin secretion. Renin catalyzes the conversion of angiotensinogen to angiotensin I in the blood. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). After binding to specific receptors (classified as either AT1 or AT2 subtypes), angiotensin II exerts biologic effects in several tissues. The AT1 receptor is located in brain, kidney, myocardium, peripheral vasculature, and the adrenal glands. These receptors mediate most responses that are critical to cardiovascular and kidney function (Sasen & Maclaughlin, 2008).

This study calculates that no one of the patients got definite ADR. 30 patients got possible and 11 patients got probable ADRs (Table 2). The rest of the patients did not get any ADR. Adverse drug reactions (ADRs) are the most frequently reported cause of adverse events during hospitalization accounting for nearly 20 percent (Oberg, 1999) . It is estimated that up to 20 percent of all hospitalized patients suffer at least one ADR during their stay.

Table 2. Adverse Drug Reactions

ADR	N	(%)
Doubtful	159	79.5
Possible	30	15.0
Probable	11	5.5
Total	200	

Table 3 shows most of the drugs that cause ADRs in ESRF patients are insulin (3.5%), nifedipine (3%), and gliclazide (2.5%). Insulin is is a hormone secreted by the beta cells of the pancreatic islets of Langerhans; commercially available insulin preparations are classified as rapid-acting, short-acting, intermediate-acting, or long-acting (Sweetman, 2007). Insulin was used by sliding scale method. Use of such sliding-scale regimens treats existing hyperglycemia rather than preventing its occurrence and may lead to rapid changes in blood glucose levels, which exacerbates both hyperglycemia and hypoglycemia. In addition, studies have found that sliding-scale insulin regimens prescribed upon hospital admission are likely to be used throughout the hospital stay without modifications for risk factors for hypoglycemia or hyperglycemia, prehospital insulin treatment regimens, or patient's sensitivity to insulin (Sweetman, 2007).

Gliclazide belongs to Sulphonylureas. Gliclazide was use for diabetes mellitus type 2 treatment 40–80 mg daily, adjusted according to response up to 160 mg as a single dose, with breakfast, higher doses divided twice into 320 mg daily. Gliclazide may be used in renal impairment, but careful monitoring of blood-glucose concentration is essential. Control was required to choose the smallest possible dose that produces adequate control of blood glucose(Departments, 2008).

Table 3. Drug Which Cause Adverse Drug Reaction

Drugs	N	(%)
None	160	80.0
Gliclazide	5	2.5
Vancomycine	4	2.0
Metoprolol	2	1.0
Cefuroxime	1	0.5
Allopurinol	1	0.5
Nifedipine	6	3.0
Insulin	7	3.5
Calcium carbonate	3	1.5
ISDN+metoprolol+perindopril	1	0.5
Tamoxifen	1	0.5
Felodipine	1	0.5
Amlodipine+furosemid	1	0.5
Furosemid+nifedipine+perindopril	1	0.5
Furosemide+losartan+HCT	1	0.5
Heparin	1	0.5
Amlodipin	2	1.0
Furosemid	1	0.5
Tramadol	1	0.5
Total	200	

Nifedipine was a dihydropyridine calcium-channel blockers. It inhibits movement of calcium ions across cell membrane in systemic and coronary vascular smooth muscle and myocardium (Departments, 2008). Short-acting formulations of nifedipine are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia (Departments, 2008). Table 3 shows the major case of adverse drug reaction was hypoglycemia because admission of insulin. Other kinds of Adverse Drug Reactions given in table 4. Hypoglicemia was signed by anxiety, chills, confusion, cool and pale skin, drowsiness, excessive hunger, headache, irritability, nausea, rapid pulse, tremors. Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual patient. For patients with acute-onset diabetes, treatment should be started with a-short-acting insulin (e.g. soluble insulin, insulin aspart) given 3 times daily with intermediate-actin insulin at bedtime. For those less severely ill, treatment is usually started with a mixture of premixed short- and intermediate-acting insulin (most commonly in a proportion of 30% soluble insulin and 70% isophane insulin) given twice

daily; eight units twice daily is a suitable initial dose for most ambulant patients. The proportion of the short-acting soluble component can be increased in those with excessive postprandial hyperglycaemia.

Table 4. Kinds Of Adverse Drug Reactions

Kinds of ADRs	N	(%)
None	160	80.0
Increase creatinine level	2	1.0
Headache+dysuria	1	0.5
Nausea+vomitting	3	1.5
Lethargy	2	1.0
Itchy	2	1.0
Bone marrow depression	1	0.5
Edema+short of breath	4	2.0
Hypotension+lethargy	7	3.5
Hypoglicemia	11	5.5
Fluid overload	2	1.0
Hypercalcemia	3	1.5
Thrombocytophenia	1	0.5
Hypovolemia+hipokalemia	1	0.5
Total	200	

The dose of insulin is increased gradually, taking care to avoid troublesome hypoglycaemic reactions (Departments, 2008).

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