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Research Article

ROLE OF CLINICAL PHARMACIST IN DOSE ADJUSTMENT OF RENALLY ELIMINATED DRUGS IN CARDIAC PATIENTS WITH RENAL IMPAIRMENT

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ABSTRACT

Introduction: Clinical pharmacist role in dose adjustment of renally eliminated drugs is crucial to prevent or decrease drug-related adverse events and eventually decrease hospitalization and costs. Materials and method: to address correct dosing and the avoidable adverse events, the incidence of renal impairment following cardiac surgery was evaluated to guide the pharmacist and the cost impact of dose adjustment were calculated accordingly. Clinical outcome will not be assessed since the adverse event were avoided by dose adjustment. Result and discussion: from all admitted patients to 160-full bed capacity tertiary hospital for different cardiac procedures, eighty-eight met the inclusion criteria and followed for four weeks. Only 35.6% preserved normal kidney function while the rest developed acute renal impairment. Dose adjustment was recommended for 13.8% of the patients and involved six drugs. all dose recommendations were agreed by the physicians with estimated annual saving of 384,358 Saudi riyals. Conclusion: clinical pharmacist monitoring prescriptions for dosing error decreases the total cost and may prevents incidence of drug related adverse effects.

KEY WORDS: Clinical pharmacy, Intervention, Dosing, Pharmaceutical care.

INTRODUCTION

Acute renal failure is classified into three categories; prerenal azotemia, intrinsic renal azotemia and post renal etiologies. Prerenal azotemia, a physiological response to renal hypoperfusion in which the integrity of renal tissue is preserved. Intrinsic renal azotemia (acute tubular necrosis), acute damage of renal tissue is induced by nephrotoxic drugs or ischemia. Post renal etiologies are urologic problems (due to obstruction, diabetes, or recurrent urinary tract infection). In all types of acute renal failure, the potassium level is increased since it is excreted renally causing lethal cardiac arrhythmias[1]. Patients with cardiac events or problems or those undergoing heart surgery may experience impaired renal function. This impairment is usually associated with increased morbidity and mortality due to the decrease in cardiac output that will decrease renal perfusion, and it is leading for worsening of those already renally impaired[2].
Patient characteristics related to increased risk of acute renal failure are sometimes severe enough to require dialysis including aging (>65 years old), high preoperative serum creatinine SCr (>100 umol/L), congestive heart failure, ejection fraction less than 50%, extent of disease, cardiac procedure [coronary artery bypass grafting, valve(s) or both] and cardiopulmonary bypass duration (>90 minutes)[3-5].

Effect of renal impairment on drug disposition especially for renally eliminated drugs is due to decreased clearance, tubular secretion or reabsorption. It is important to reduce dose of certain drugs if the serum creatinine increases by 0.6 mg/dL/day. This indicates 25% to 30% loss of renal function. The most important factors for patients with renal impairment include: serum albumin levels (major binding protein for many drugs such as digoxin). In case of hypoalbuminemia (such as diabetic patients with advanced renal disease) toxic levels are predicted also for NSAIDs as more free form of the drug is much higher. Secondly, creatinine clearance CrCL that decreases with the age at a rate of 1 ml/min/year between the ages of 30 to 60 due to the decrease in muscle and nephron mass. Thirdly, volume depletion induced by some drugs such as gentamicin is a risk factor for renal failure. Furthermore, if patients are already with intravascular volume depletion, they would be more susceptible to toxicity, or if they undergo dialysis that places them at increased risk of infection then the use of antibiotics is required. Another factor is the cardiac function, as discussed before, decreases the renal perfusion and makes patients prone to toxicity of certain drugs such as angiotensin converting enzyme inhibitors and NSAIDs. And finally, Ideal body weight (IBW) should be calculated especially for obese patients as it is a major determinant of volume of distribution. In patients with low body weight, the actual body weight should be used for the estimation of clearance rather than IBW[5-8].

The renal function and severity of impairment are usually assessed by the following: estimating CrCL, measuring blood urea nitrogen (BUN), BUN/Creatinine ratio. The increase in both measures (BUN and BUN/Creatinine ratio) indicates systemic hypoperfusion rather than intrinsic renal dysfunction in the absence of conditions that enhance urea production, such as gastrointestinal bleeding, corticosteroid therapy, or a high-protein diet[2,9]. Serum creatinine levels rise only if glomerular filtration rate (GFR) is markedly reduced and thus the equation proposed by Cockcroft and Gault (CrCL estimation rather than depending on SCr level only) is frequently used in practice and correlates well with sensitive measurements of glomerular function.

In renal impairment, the dose adjustment of renally eliminated drugs is required to prevent drug accumulation and thus avoiding of toxicity or decreasing drug-related adverse effect and decreasing hospitalization stay and costs[10]. An important example of the effect of moderate renal impairment, digoxin therapy was

associated with more than a twofold increase in the risk of primary cardiac arrest that offset its benefit in patients with congestive heart failure so, dose reduction is critical in this case[11]. In addition, renal replacement therapy RRT may complicate therapy and leads to under- or overdosing[12].

Having clinical pharmacist during physician rounds will decrease preventable adverse drug events especially in intensive care unit. Adverse drug events were the sixth leading cause of death in USA in 1994 with 10.9% of all hospital patients. A list of safe and cost-effective medications must be identified. Most of interventions made by clinical pharmacist are through adjustment of dose or frequency coming first and laboratory monitoring. Pharmacists working beside the dispensing windows miss the opportunity to analyzing patient problem and thus become less able to assist physicians in rational prescribing. Also, on-call pharmacist may not be efficient in this regard as they are distant from the decision-making process. Addressing medical errors is one strategy to improve safety of medication[13] Requirements for clinical pharmacist for promotion includes interpretation of laboratory values and pharmacokinetics[14] and this study depends on these.

The contribution of clinical pharmacy services is difficult to be measured but for sure it is beneficial since it covers prescription monitoring, reduction in length of hospital stays and incidence of adverse drug reactions and in total cost[15]. A 6-Month creatinine clearance dosing adjustment program conducted in Albany Medical Center Hospital, USA in 1995 resulted in a total cost avoidance of $11,702.08[16]. Six clinical pharmacists at Barnes-Jewish Hospital (1200-bed teaching hospital) recorded all interventions done for 30 days and extrapolated an annual savings of $394,000 (95% confidence interval, $46,000-$742,000)[17]. A review of the economic benefit of clinical pharmacy services through 59 articles published between 1996 to 2000 performed by Center for Pharmacoeconomics Research and Department of Pharmacy Practice, University of Illinois at Chicago, USA, estimated that $45.6 billion in direct health care costs would be avoided even when this kind of service led to 4-fold increase in fee association. For every dollar invested in clinical pharmacy services, $4 in benefit is expected provided that this kind of service has positive financial benefits[18].

Through clinical observation, patients with cardiac problems were in high risk to develop renal impairment. In this study we were interested in assessing the role of clinical pharmacist in dosage adjustment in these patients and the cost impact of such a service.

The main objectives of the study: addressing renal function as a tool for appropriate dosing and determining whether physicians calculate CrCL for dosing. Other objectives: determine the incidence of renal impairment in hospitalized patient with cardiac problems or undergoing cardiac procedure and the cost impact of clinical pharmacist interventions.

MATERIALS AND METHOD

The study was conducted at Prince Sultan Cardiac Center in Riyadh, Kingdom of Saudi Arabia, a 160 full-capacity beds instituted for hospitalized patients with cardiac problems or scheduled procedures (with 5304 admissions per year) and also serve outpatient and emergency clinics. This prospective, observational and interventional study was performed for four weeks during July 2004 five days a week. Through Pharmacy and Therapeutic Committee (P&T), the PSCC pharmacy proposed establishing a renal dosing and monitoring services in which the hospital formulary was reviewed and drugs which are subjects for dosing adjustment in renally impaired patients were identified along with the required adjustment in such a case, the service was approved by the P&T committee to be provided by PSCC pharmacy department. A list of drugs comprises: ceftazidime, cefuroxime, ciprofloxacin, digoxin, gentamicin, meropenem, piperacillin/tazobactam (tazocin), ranitidine, vancomycin, and others were monitored. The list was selected based on extensive use and high acquisition cost.

Patients and Interventions

The clinical pharmacist identified patients receiving these drugs on daily basis, reviewed their demographic data and assessed their laboratory findings. The appropriate dosing adjustment was recommended according to renal function status. Some of these drugs required monitoring the serum level for appropriate dosing, and culture sensitivity but parallel to the degree of renal impairment, recommendation of dosing depends in information approved by P&T committee. The documentation of whether the recommendation has been accepted or not, or any reevaluated dose according to renal function were considered as a new intervention.

Cost avoidance was determined by calculating the difference between the costs of the original and adjusted regimens. From ethical point of view because we believe that patient care coming first in the priority of clinical pharmacy services we can't apply intervention versus non-intervention groups in patients developing renal impairment, we assumed that the original regimens prescribed by physicians were the non-interventional and the adjusted regimens suggested by clinical pharmacists were the interventional in cost avoidance calculation. Drug administration devices, pharmacist time in monitoring, nursing administration, pharmacy preparation, if any, have not been included in these calculations. Cost incurred due to recommendation to increase dose should not be included because this what the patient should take according to the recognized treatment plan. We did not assess the clinical outcome, but it is believed that if the given dose is comparable to that in someone with normal renal function there will be an optimal effect without adverse events. In the design and study calculation, the suitable pharmacoeconomic principles have been implemented[19-23].

Inclusion Criteria

Only the following patients were included in the study: all hospitalized cardiac patients eighteen years of age or older, receiving one or more of the study medications and patients undergoing dialysis.

Exclusion Criteria

The following patients were excluded from the study: below eighteen years of age and patients not receiving any of the study medications.

Data Collection

The clinical pharmacist monitored all hospitalized patients above 18 years old on one or more of the following drugs: ceftazideme, cefuroxime, ciprofloxacin, digoxin, gentamicin, meropenem, piperacillin/tazobactam (tazocin), ranitidine, vancomycin, followed them up for the required duration of therapy. Reviewed their demographic data [age, sex, weight, height]. Recorded BUN, BUN/creatinine ratio and other important laboratory findings such as electrolytes (potassium). The ideal body weight (IBW) has been estimated for each subject. If the actual body weight is less than the IBW, then the actual was used in calculation of CrCL using Cockcroft and Gault equation (table 1). A CrCL $\geq$ 50 ml/min was considered normal, less than 50 or on dialysis was included in the study taking into consideration the type of the dialysis. To calculate CrCL for patients older than 60 with apparent normal serum creatinine, 30 were subtracted from

patient's age and the result of CrCL from 110 ml/min. Incidence of renal impairment among all screened patients has been calculated. Severity of heart events, underlying disease (such as IDDM), ejection fraction and cardiac output, procedure type [CABG, valve(s) or both, number and duration], and pharmacotherapy (digoxin, diuretics, etc.), diagnosis for which the target drugs being prescribed were recorded. Routine daily review of drug order sheet, suggestion of an appropriate dosing regimen in case of under- or overdosing either by dose and/or interval adjustment have been carried out. A dosage adjustment depends on renal function estimated by CrCL, serum level of some drugs, culture sensitivity when applicable taking into consideration $M1C_{90}$, type of dialysis and filtrate pore size. Action(s) taken by physicians either by agree, disagree or change but with modification were recorded. Calculation of cost avoidance and extrapolation of the results to one year have been performed.

Statistical Analysis

Variables have been coded individually, and data were analyzed using the Statistical Package for Social Sciences (SPSS) version 13.0 for Windows (SPSS Inc., Chicago, Illinois). Agreements between physician's and pharmacist's assessments have been evaluated. Statistical significance defined as $p \leq 0.05$.

Ethics Approval

The study was approved by the Ethical Committee in PSCC and according to Helsinki Declaration and the safety of all patients was insured.

Table 1: Equations for calculating ideal body weight and creatinine clearance CrCL

Ideal body weight IBW
IBW (male) = 50.0 + (2.3 x height in inches over 5 feet). IBW (female) = 45.5 + (2.3 x height in inches over 5 feet)
Creatinine clearance using Cockcroft and Gault equation CrCL
CrCL (male) = $\frac{(140-\text{age}) \text{x IBW}}{72 \text{ X SCr}}$ CrCL (female) = 0.85 x CrCL (male) Where, CrCL is the creatinine clearance in ml/min, age in years, W is the IBW in kg and SCr is the serum creatinine in mg/dl Use IBW unless the patient actual body weight is less than IBW.

Table 2: Demographics

	Male	Female	P (sig.)*
Age	52.9±15 (N=45)	52±15 (N=42)	0.773 (NS)
Weight by Kg	44±17 (N=44)	63.2±12.6 (N=42)	0.001 (S)
Ideal body weight by Kg (IBW)	63.5±5.6 (N=42)	64.3±98.3 (N=39)	0.959 (NS)
Height by cm	77.5±35 (N=43)	79.5±38.5 (N=38)	0.839 (NS)

* S= Significant, NS= Not Significant

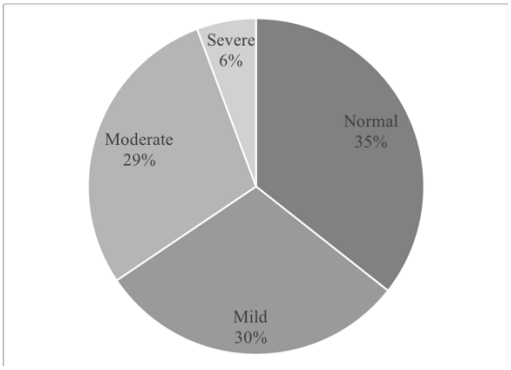

Fig. 1: percentage of patients by renal impairment categories

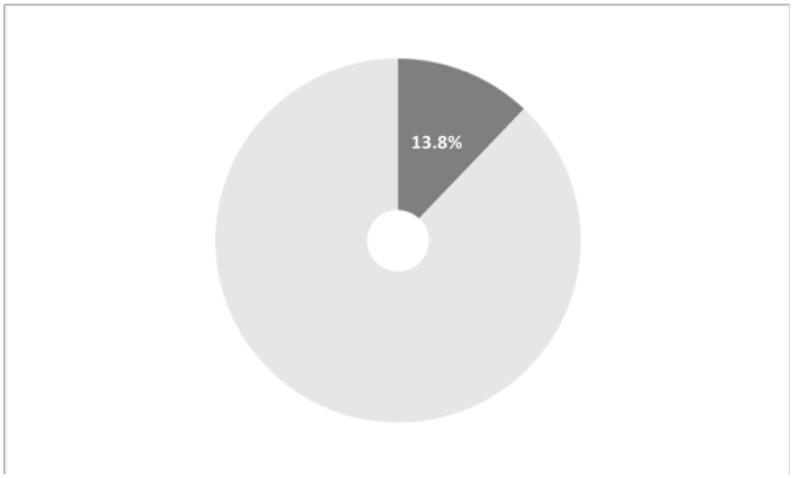

Fig. 2: Percentage of patients required dose adjustment

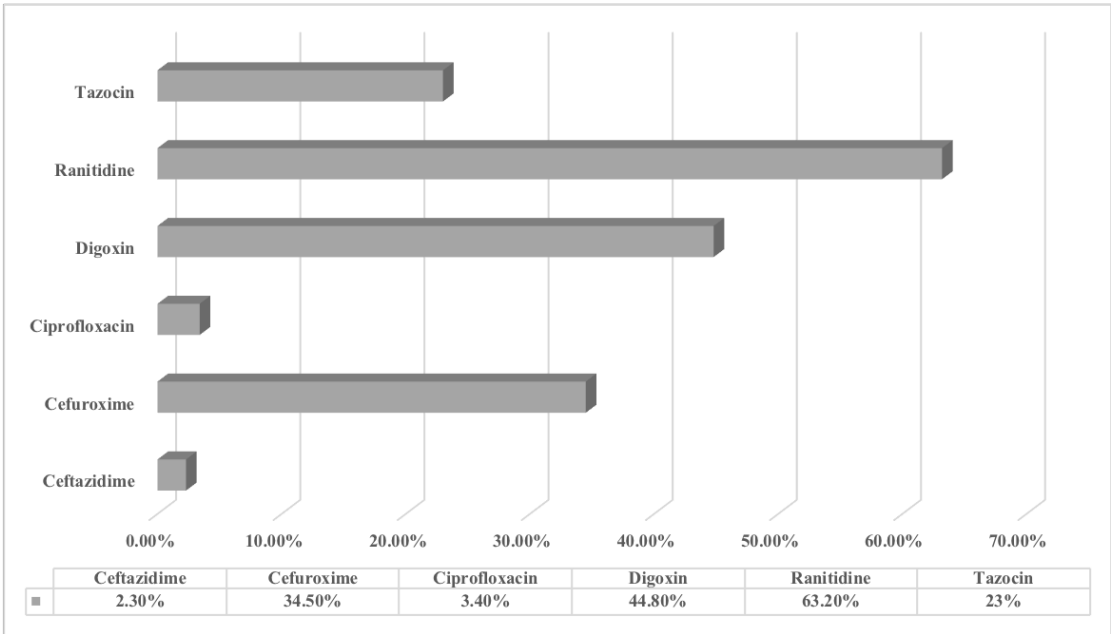

Fig. 3: Drugs involved and required adjustment (%)

RESULT AND DISCUSSION

From all admitted patients, eighty-eight met the inclusion criteria, their demographics (age, gender, and IBW) were not significant between subjects (Table 2 summarize their demographics). 57.5% were in the intensive care unit and 27.6% had congestive heart failure. According to renal impairment categories, only 35% were with normal kidney function. Renal impairment was mild for 30%, moderate for 29% and severe for 6% of patients (Fig. 1). Doses of the six drugs involved in the study were incorrect and adjusted for 13.8% of the patients. Ranitidine dose adjustment came first with 63.2%, Digoxin in the second place with 44.8%, cefuroxime with 34% of the adjustments, Tazocin with 23% and lastly, Ciprofloxacin and Ceftazidime with 3.4% and 2.3% respectively (Fig. 2 and 3), all recommendations were agreed by the physicians with 100% satisfaction and dosing were made accordingly. Cost avoidance calculated during the study was then used to estimate an annual saving of 384,358 Saudi riyals (102,439 United states dollar). The estimated cost savings consider number of annual hospital admissions and drug cost only without hospital stay and service cost, pharmacy monitoring, preparations and nursing administration which in return if have been accounted in calculations would lead to more cost savings.

CONCLUSION

Clinical pharmacist role in monitoring prescriptions for correct dosing decreases total cost and may prevents incidence of adverse events.

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