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 on SCr level only) is frequently used in practice and correlates with sensitive measurements of glomerular function.

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 diet5-9. 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 costs10. 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 offsets its benefit in patients with congestive heart failure so, dose reduction is critical in this case\textsuperscript{11}. In addition, renal replacement therapy RRT may complicate pharmacy department. A list of drugs comprises: cefazidime, 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 we have assumed that 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\textsuperscript{18-23}.

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: cefazidime, 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) used in calculation of CrCL for patients older than 60 years of age was estimated \textsuperscript{17}.

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 institute 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.
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 M1C90, 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

<table>
<thead>
<tr>
<th>Equation</th>
<th>Formula</th>
</tr>
</thead>
</table>
| Ideal body weight IBW | \( \text{IBW (male)} = 50.0 + (2.3 \times \text{height in inches over 5 feet}) \)  
\( \text{IBW (female)} = 45.5 + (2.3 \times \text{height in inches over 5 feet}) \) |
| Creatinine clearance using Cockcroft and Gault equation CrCL | \( \text{CrCL} = \left( \frac{140 - \text{age}}{72 \times \text{SCr}} \right) \times \text{W} \)  
\( \text{CrCL (male)} = 0.85 \times \text{CrCL (male)} \) |

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male</th>
<th>Female</th>
<th>( \text{P (sig.)}^{*} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52.9±15 (N=45)</td>
<td>52±15 (N=42)</td>
<td>0.773 (NS)</td>
</tr>
<tr>
<td>Weight by Kg</td>
<td>44±17 (N=44)</td>
<td>63.2±12.6 (N=42)</td>
<td>0.001 (S)</td>
</tr>
<tr>
<td>Ideal body weight by Kg (IBW)</td>
<td>63.5±5.6 (N=42)</td>
<td>64.3±9.8 (N=39)</td>
<td>0.959 (NS)</td>
</tr>
<tr>
<td>Height by cm</td>
<td>77.5±35 (N=43)</td>
<td>79.5±38.5 (N=38)</td>
<td>0.839 (NS)</td>
</tr>
</tbody>
</table>

\( S= \text{Significant}, \ NS= \text{Not Significant} \)

### Fig. 1: Percentage of patients by renal impairment categories

### Fig. 2: Percentage of patients required dose 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 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).

CONCLUSION

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

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