A survey on the appropriateness of drug therapy in patients with renal dysfunction at the Internal Medicine Ward FMUI/Dr. Cipto Mangunkusumo Hospital

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Abstrak

Tujuan *Penyesuaian dosis dan pemilihan jenis obat penting dilakukan dalam keadaan gangguan fungsi ginjal. Penelitian observasional ini bertujuan untuk mengetahui ketepatan penyesuaian dosis dan ketepatan pemilihan obat pada pasien di ruang rawat inap Departemen Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia/Rumah Sakit Dr. Cipto Mangunkusumo, Jakarta*

Metode *Pasien usia 18 tahun atau lebih dengan bersihan kreatinin <60 mL/menit berdasarkan rumus Cockroft-Gault diikutkan dalam penelitian ini. Obat yang dinilai adalah obat yang ekskresinya terutama melalui ginjal dan obat-obat yang bersifat nefrotoksik. Ketepatan pemilihan dinilai berdasarkan ada/tidaknya kontraindikasi dan interaksi potensial antar obat yang digunakan, sedangkan ketepatan penyesuaian dosis didasarkan pada berbagai literature buku teks dan brosur obat. Data dikumpulkan antara bulan May sampai July 2007.*

Hasil *Dari 43 pasien yang memenuhi kriteria inklusi, didapatkan pemakaian obat sebanyak 385 jenis, 164 jenis di antaranya mempunyai jalur ekskresi utama di ginjal dan/atau bersifat nefrotoksik. Dari 164 jenis obat tersebut, penyesuaian dosis dilakukan dengan tepat pada 142 jenis obat (86.5%), sedangkan penyesuaian yang tidak tepat terdapat pada 22 jenis obat (13.5%). Terdapat 1 pemakaian obat yang merupakan kontraindikasi, dan 15.1% dinilai potensial berinteraksi.*

Kesimpulan *Penyesuaian dosis dan pemilihan obat pada pasien gangguan fungsi ginjal di ruang rawat inap Departemen Ilmu Penyakit Dalam Fakultas Kedokteran Universitas Indonesia/Rumah Sakit Dr. Cipto Mangunkusumo telah dilakukan dengan baik.* **(Med J Indones 2009; 18: 108-13)**

Abstract

Aim   Dose adjusment and drug selection is important in patient with renal dysfuction.This study was aimed to assess the accuracy of dose adjustment and drug selection for renal dysfunction patient at the Internal Medicine Ward FMUI/Dr. Cipto Mangunkusumo Hospital, Jakarta

Methods   Patients ≥ 18 years old with estimated creatinine clearance < 60 mL/minute based on Cockroft-Gault formula were included in this study. The drugs assessed were those excreted by the kidney or having nephrotoxic effect. The appropriateness of drug selection is assessed based on the preserce or not contraindication or potential of drug-drug interaction. The accuracy of dose adjustment were assessed based on information available in various textbooks, literatures, and drug brochures. Data were collected between May to July 2007.

Results   Data obtained from 43 patients met the inclusion criterias demonstrated that 164 out of 385 drug prescriptions were mainly eliminated by the kidney or have nephrotoxic characteristic. Out of 164 drug prescriptions, 142 (86.5%) were appropriately adjusted, while the other 22 (13.5%) were inappropriately adjusted for the dose. There was only one contraindication for the usage of the drug and 15.1% potentially drug interaction.

Conclusion   Dose adjustment and drug selections in patients with renal dysfunction at the Internal Medicine Ward FMUI/Dr. Cipto Mangunkusumo Hospital are conducted appropriately. **(Med J Indones 2009; 18: 108-13)**

Key words: *renal dysfunction, drug interaction, contraindication, dose adjusment*

The kidneys are organs which play important roles in regulating volume and composition of the body fluid, and eliminated many drugs and waste products of metabolism process.[1-4]

Many drugs are excreted by the kidney through glomerular filtration (e.g. ceftazidime, gentamicin), tubular secretion (e.g. penicillin), or a combination of these processess (e.g. ampicillin, acyclovir). A number of important drugs are primarily excreted unchanged or as active metabolites and if renal function is impaired, this will have important consequences for drug therapy[5,6]

The central role of the kidney in the removal of drugs and metabolites makes it susceptible to adverse drug effects. Renal dysfunction can cause accumulation ofmost drugs and their active metabolites and can sometimes induce nephrotoxicity. For many drugs, dosage adjustment according to renal function is indicated in order to avoid overdosage, to maximize therapeutic efficacy, and minimize adverse drug reactions.[5, 7]

In order prevent accumulation of drugs and their active metabolites in the body, doses of some drugs, especially those which mainly eliminated by the kidney and have a narrow margin of safety, must be adjusted to therapentic concentration while avoiding toxic effect. Kidney junction is commonly estimated using Cocroft-Gault formula based on serum creatinine, age body weight and gender. Dose adjusment can be done by using a nomograms, calculatingby formula, or based oninformation in drug brochures or data from literature or textbooks.Implementation of dose adjusment can be done by reducing the dose or by interval of drug administration.[6,8-10]

The aim of this study was to assess the accuraracy of drug selection and dose adjusment in hospitalized patients with renal dysfunction.

METHODS

Design

This is a cross-sectional observational study conducted at the Internal Medicine Ward Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia, Jakarta.

This study was approved by the Committee of The Medical Research Ethics of the Faculty of Medicine, University of Indonesia.

Subjects

From May to July 2007, data from patients age $\geq$ 18 years old in both gender and with estimated creatinine clearance of < 60 mL/minute based on Cockroft-Gault formula were collected. Patients under hemodialysis or CAPD (Continuous Ambulatory Peritoneal Dialysis) were excluded from this study. The following parameters were collected for all patients with renal dysfunction: age, gender, serum creatinine, weight, date of first time hospitalization, the doses and the type of drug selected. The accuracy of dose adjustment, contraindication (if any), and potential drug interaction were assessed based on various literatures, textbook, , and drug brochures. Each medication were classified as 'appropriate' when the dosage and the choice were appropriate with the degree of renal dysjunction and as considered'inappropriate' when the dosage prescribed was not in conformity with the adjustment required in the textbook or literature with regard to renal function. Medication were classified as 'contraindication' and 'as having potential interaction' if (The literature of reference) mentioned a contraindication or drug interaction each other.

Analysis

All data were assessed by descriptive statistical analysis and were presented in the tabular and textual form.

RESULTS

A total of 43 patients were included in this study. Of these, 33% were male and 67.4% were female, with a median age of 52 years, mean serum creatinine level of $3,4 \pm 4,2$ mg/dL (range 0.8-18.5 mg/dL), and mean estimated creatinine clearance of $26,06 \pm 12,44$ mL/minute (range 3.51-53.40 mL/minute) (Table 1).

Table 1. Characteristic of patients recruited in this study

Parameter	Number
N	43
Age, mean±SD (median),year	51±15(52)
Male, n (%)	14 (33)
Female sex, n (%)	29 (67.4)
Serum creatinine, mg/dL (median)	3.4±4.2 (2.0)
Clearance creatinine, mL/min (median)	26.06±12.44 (25.25)
Drugs prescribed per patients, mean±SD	9±4.2

Three-hundred and eighty-five drugs were prescribed for these 43 patients. Forty-three per cent (164 of 385) were primarily eliminated through the kidney and had a nnephrotoxice characteristics.

The appropriateness of these 164 drugs were depicted in table 2. Eighty-six per cent (n=141) were appropriate, while 13% (n=22) had inappropriate dosage with regards to the patient's renal function and 1 drug was contraindicated. Some drugs that had not been adjusted to the degree of renal dysfunction, the dose was always too high. Drugs often prescribed in excessive doses included antibiotics, allopurinol, fluconazole, and antituberculosis (Table 3). Drug which was contraindicated was metformin.

Table 2. Appropriateness of dose adjustment

Appropriateness	12 (%)
Appropriate	141 (86%)
Overdosage	22 (13%)
Contraindication	1
Total	164

Table 3. Drugs with inappropriate adjustment

	Drugs	Frequency	clcr	Dosage given	Recommended dose
1.	Ceftazidime	5	21.6	2x1g/d	1x1g/d
			22.3	3x1g/d	1x1g/d
			35.4	3x1g/d	2x1g/d
			21.2	2x1g/d	1x1g/d
			34.2	3x1g/d	2x1g/d
2.	Levofloxacin	2	18.9	1x500mg/d	1x250mg/d
			13.4	1x500mg/d	1x250mg/d
3.	Amikacin	1	22.3	1x500mg/d	200-450mg/d
4.	Streptomycin	2	52.2	1x750mg/d	1x350mg/d
			32.8	1x750mg/d	1x250mg/d
5.	Tetracycline	1	28	3x500mg/d	2x500mg/d
6.	Ethambutol	2	24.8	3x250mg/d	3x500mg 3x/week
			18.9	3x250mg/d	1-1.5g 3x/week
7.	Pyrazinamide	1	24.8	3x250mg/d	3x250mg 3x/week
8.	Ranitidine	1	26.4	2x150mg/d	2x100mg/d
9.	Allopurinol	3	18.9	1x300mg/d	50-100mg/d
			35.4	1x300mg/d	1x100mg/d
			24.9	1x300mg/d	50-100mg/d
10.	Fluconazole	3	22.3	2x50mg/d	1x25mg/d
			34.2	1x200mg/d	1x25mg/d
			52.2	1x200mg/d	1x25mg/d
11.	Imipenem	1	22.9	3x500mg	2x500 mg
	Total	22			

clcr : creatinin clearance

Table 4. Potential drug interaction

Drug I	Drug II	Drug III	Total use
Captopril	Allopurinol	-	3
Captopril	Metformin	Insulin	1
Captopril	Insulin	-	10
Captopril	Spironolactone	-	1
Captopril	KSR	-	7
Captopril	Spironolactone	KSR	2
Captopril	Aspirin	-	12
CaCO$_3$	Ciprofloxacin	-	1
Ferrous Sulfate	Ciprofloxacin	-	1
CaCO$_3$	Ciprofloxacin	Ferrous Sulfate	1
CaCO$_3$	Levofloxacin	-	3
CaCO$_3$	Levofloxacin	Ferrous Sulfate	1
Rifampicin	Propranolol	-	1
Rifampicin	Simvastatin	-	2
Rifampicin	Fluconazole	-	1
Rifampicin	Nifedipine	-	1
Phenytoin	Fluconazole	-	1
Phenytoin	Nifedipine	-	1
Warfarin	Allopurinol	-	1
Warfarin	Metronidazole	-	1
Warfarin	Heparin	Aspirin	1
Digoxin	Furosemide	-	4
Pyrimethamine	Cotrimoxazole	-	1
Total			**58**

Note. KSR is a KCl slow release

DISCUSSION

Renal diseases often induce multiple pathophysiologic changes that lead to alteration in pharmacokinetic profile. Pharmacokinetics of drugs should be evaluated in patients with renal dysfunction to determine whether dose adjustment is needed to enhance tolerance and tooptimize the efficacy.[11]

This study showed that the appropriateness of drug therapy in patients with renal dysfunction at the Internal Medicine Ward Dr. Cipto Mangunkusumo hospital was satisfactory. This statement is supported by the fact that 86% of prescription were appropriate while only 13% were considered inappropriate. Several explanations for this inappropriateness might include scanty knowledge of the physician of the medications requiring adjustment in renal dysfunction, physicians' underestimation of the consequences of mild renal dysfunction, and fluctuating renal function. Rapid changing in serum creatinine values might not permit appropriate estimation of renal function.

The percentage of appropriate adjustment at Cipto Mangunkusumo hospital were higher than the study of Salomon et al in France[12] which reported 66 % and the study of Falconnier et al in Swiss[13] with 81% with well adjusted doses. This difference may be due to the status of Cipto Mangunkusumo hospital as a teaching hospital so that drug prescriptions in hospitalized patients, particularly with renal dysfunction, are closely monitored either by residence on ward or by supervisors. In this hospital, drugs known to be nephrotoxic, such as aminoglycoside were usually avoided. This may be one of the reasons contributing to the appropriate drug therapy in patients in the present study. Current practice is to give aminoglycoside in total daily dose as a single injection, although historically it was administered as two or three equally divided doses. The dose must be adjusted for patients with creatinine clearancesless than 80 to 100 mL/min and plasma concentrations must be monitored.[14] Fluconazole was the drug which has not been adjusted in this study. The primary route of elimination of fluconazole is via renal excretion. The elimination half-life may increase from 25-30 hours to up to 98 hours in patients with a creatinine clearance of <20 mL/min.15 This study also shows that metformin was the only 1 drug contraindicated to patients with renal dysfunction. Almost 90%, metformin is eliminated in the urin through glomerular filtration and tubular secretion. Metformin is contraindicated in male patients with serum creatinine ≥1.5 mg/dL and in female patients with serum creatinine ≥1.4 mg/dL.16-18 This study also shows 15% of the prescriptions are associated with potential interaction. For many patients with compromised renal function, however, this is unavoidable because these type of patients often had multipathologic conditions. In this study, one patient receive in average 9 type drugs and one patient receive 4 type drugs with main elimination in the kidney and/or nephrotoxic characteristic.

Strategies to adjust drug dosage in renal dysfunction may help to individualize drug therapy and, thus, contribute to

drug safety. Principles to increase the safety of drug prescription in patients with renal dysfunction are to select the appropriate drugs in patients with renal dysfunction, e.g. by taking into consideration the possibility of drug interaction and doses.[19,20] A stepwise approach to assist physicians in prescribing drug therapy for patients with renal dysfunction is initial assessment which includes a history and physical examination, calculates creatinine clearance, chooses a loading dose and maintenance dose, and monitoring drug level principally drugs with narrow therapeutic margin.[21,22]

There was no adverse effect related to inappropriate drug prescriptions found in this study because adverse effect can occur by multiple factors e.g. age, patient conditions, and drug prescription concomitantly. It is highly recommended that drug dose adjustment be continuosly done based on the most recent creatinine clearance data of each patient.

Measurement of creatinine clearance in patients with renal dysfunction is not the only determinant for drug dose adjustment. Other factors such as absorption, distribution, metabolism, and elimination should also be taken into consideration in drug dose adjustment.[6] Kidney disease it self may after drug metabolisme studies in rats conducted by Leblond et al. showed that chronic kidney disease is associated with decreased in liver cytochrome P450 activity (mainly in CYP2C11, CYP3A1, and 3A2), secondary to reduced gene expression.[23] Dowling et al. also assessed activity hepatic cytochrome P4503A activity in patients with end-stage renal disease and they concluded that in patients with end-stage renal disease hepatic CYP3A activity is reduced compared with activity in age-matched subjects with normal renal function.[24]

In conclusion, this study emphasizes the importance of improving the identification of patients with renal dysfunction, estimating their glomerular filtration rate, and implementing appropriate dose adjustments according to these estimates. This study also suggest other intervention which could improve patient-specific outcomes such as on-line information to assist dose guidelines, access to individuals trained in pharmacokinetics, implementation of pharmacokinetic dose consultation services in departments of pharmacy or clinical pharmacology, and daily participation of clinical pharmacologist during doctor's ward visits.

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