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The Usage of Dosing GAMA Application to Evaluate the Appropriateness of Drug Doses in Hospitalized Patients with Renal Impairment

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ABSTRACT

An application named 'Dosing GAMA' has developed for drug doses adjustment in patients with renal and hepar impairment. Dosing GAMA is targeted for clinical Pharmacists to calculate and make dose recommendations for patients, based on renal and hepatic conditions. This study aims to identify the appropriateness of drug dosage adjustment by using Dosing GAMA application in hospitalized patients with renal impairment and to determine the risk factors for the drug dose inappropriateness. This study was a retrospective observational descriptive study, cross-sectional design, used a consecutive sampling technique. The source of the data was Medical Record of hospitalized patients with renal impairment (creatinine clearance ≤50 mL/min) from 2018 of February till 2020 of March in the Academic Hospital of UGM. The names and the doses of the drugs were filled to Dosing GAMA application, and it would evaluate the appropriateness of drug doses. There were 570 drugs of 73 medical records included in this study. This study revealed Dosing GAMA could assess 144 drugs (25,6%) need to adjust, and 82 drugs (56,9%) were inappropriate doses. There were significant correlations of the age characteristic (p=0,000) and the creatinine clearance value (p=0,012) to the drugs dose appropriateness. There were inappropriate doses need to adjust in the hospital. So, the use of health-based technology expected for pharmacists to improve the use of drugs rationally.
Keywords: *Dosing GAMA Application; Drug Dose Adjustment; Renal Impairment*

INTRODUCTION

According to the results of Riskesdas in 2018, the prevalence of chronic kidney disease increases from 2% (2013) to 3.8% (2018)[1,2]. Patients with decreased kidney function will affect the elimination of drugs that are excreted through the kidneys and other pharmacokinetic processes. Thus, individual dose adjustment based on creatinine clearance values or glomerular filtration rate using special calculations need to be made in patients with decreased renal function to avoid undesirable effects. Irrational dosing will lead to drug toxicity or ineffectiveness[3].

PERMENKES RI No 72 of 2016 regarding the Standard of Pharmaceutical Services in Hospitals states that a pharmacist, in carrying out clinical pharmacy services, must assess the rationality of the drugs prescribed[4]. However, in reality, irrational administration of drug doses to patients with decreased renal function is still common[5]. This may result in the patient's clinical outcome not improving. Based on the results of the previous studies, there were several factors that influenced the suitability of the dosage given to patients with decreased kidney function, namely gender[6], age[7,8], patients with hemodialysis[9], the amount of drug used, and serum creatinine levels[8].

A computer-based marker system used for dose assessment is a complementary tool for pharmacists[10]. In 2018, a research team from the Laboratory of Pharmacology and Clinical Pharmacy UGM, Rahmawati *et al.*, had developed a Dose Adjustment Software for Patients with Decreased Kidney and Hepatic Function: Dosing GAMA. The Dosing GAMA application has obtained an Intellectual Property Rights (Hak Kekayaan Intelektual) certificate with registration number 000127903[11]. The development of this application was intended to facilitate health workers, especially clinical pharmacists in hospitals, in calculating and recommending dosages according to the patient's kidney and liver condition. At the moment, the Dosing GAMA application is still in the stage of

refinement through several test stages before being widely used. The Dosing GAMA application can be easily accessed via a computer or smart phone connected to the internet. This application is equipped with features such as a login and logout system, a dashboard, data management and patient visits, and drug data settings. The Dosing GAMA is also equipped with facilities for calculating Body Mass Index (BMI), Body Surface Area (BSA), and Creatinine Clearance (CrCl) with the Cockcroft Gault formula automatically, as well as monitoring information on drug use therapy that can be used as a reference for users to perform monitoring the effectiveness of therapy. Determination of the dosage recommendation for Dosing GAMA is available in two criteria, namely based on reference and calculation of pharmacokinetic formulas that are adjusted to individual pharmacokinetic parameters using the Giusti - Hayton method.

Several studies had been conducted regarding the Dosing GAMA Application. Research conducted by Hajma (2020), regarding the use of Dosing GAMA in a group of pharmacists in making dose adjustments, showed that the use of the Dosing GAMA application had been proven to reduce the time to evaluate the dose adjustment by an average of 13.81 ± 0.781 minutes. This time was shorter than the pharmacist who evaluated the dose adjustment manually (without using the application), which was 27.50 ± 1.23 minutes ($p < 0.05$). In addition, based on the results of the usefulness test for Dosing GAMA using the Post-Study System Usability Questionnaire (PSSUQ), it showed its high benefit and was able to be accepted by pharmacists[12]. However, studies regarding the use of this computer-based system in dose adjustment in hospitalized patients with decreased renal function have not been carried out. The purpose of this study is to identify the suitability of drug doses using the Dosing GAMA Application in hospitalized patients with decreased kidney function. This study also aims to determine the factors that influence the emergence of drug dose mismatch problems in hospitalized patients with decreased kidney function.

METODE

Research Design

This research is a descriptive observational study with a cross-sectional study design. The data were collected retrospectively.

The subject of research

The sampling was done using a consecutive technique.

The consecutive technique is one of the non-probabilistic sampling methods, in which includes every patient who meets the study criteria as the study sample.[13] The data was collected through tracing the medical records of inpatients at UGM Hospital Yogyakarta for the period February 2018-March 2020. The criteria for the patient medical records in this study were patients with decreased renal function (creatinine clearance value ≤ 50 mL/min) and patient age ≥18 years. In this study, 73 medical records were obtained with 107 serum creatinine examination data (in one patient's medical record it could consist of one or more serum creatinine tests) with a total of 790 drugs used. A total of 220 names of drugs were not listed in the Dosing GAMA application. Therefore, the dosage suitability evaluation was carried out on a total of 570 drugs using the Dosing GAMA application.

Evaluation of dose suitability using the Dosing GAMA application

The dosage suitability evaluation was carried out using the Dosing GAMA application. To open the Dosing GAMA application, logging in using the appropriate user and password was needed. Patient data was then added to the 'add patient' application menu including the patient's name (initials), sex, and date of birth. Then, in the 'add visit' menu, information on the patient's visit date, serum creatinine, body weight, and diagnosis

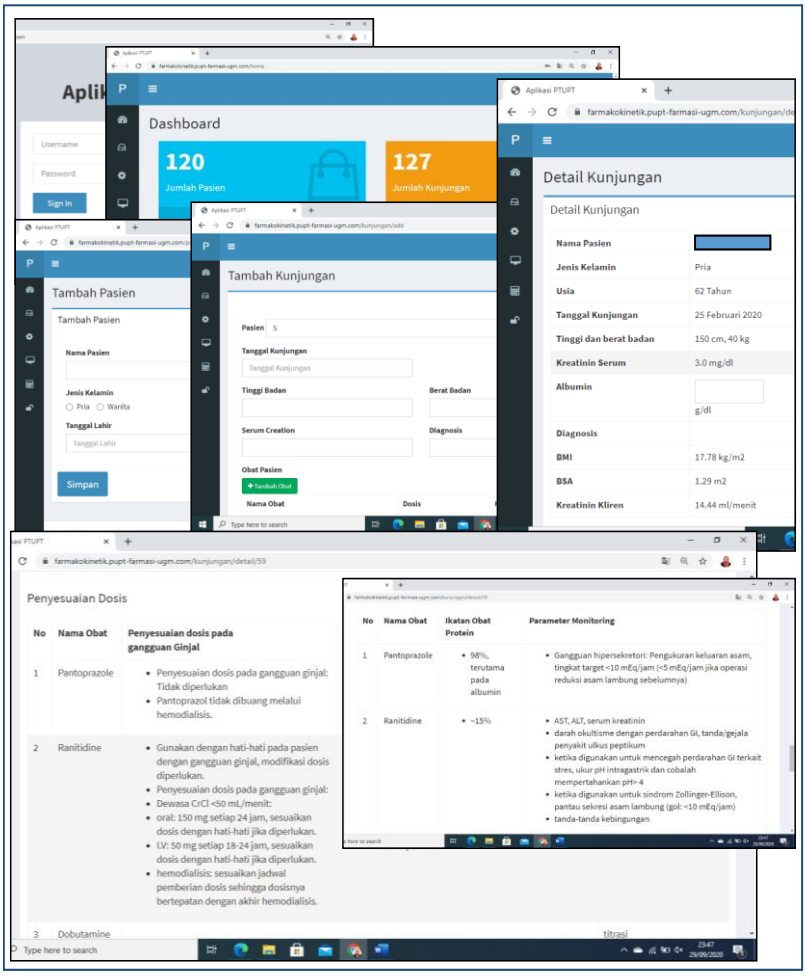

Figure 1. Example of a dosage suitability evaluation display using Dosing GAMA application

was added, as well as drug use data including the name of the drug, the drug dosage, and additional information needed. The results of data that had been entered in the application can be seen in the 'visit details' menu. The dosage recommendations based on the information given will be displayed automatically in the table of 'dose adjustment in renal impairment' in the Dosing GAMA application. In addition, this application will also display information on the appropriate drug use monitoring parameters. Figure 1 shows the information on the Dosing GAMA application in the process of evaluating drug dose adjustments in patients with renal and hepatic disorders.

Data Analysis

The collected data were analyzed using descriptive statistics to present the results of the drug dose assessment and the bivariate test to determine the relationship between dose suitability and patient characteristic data, using Statistical Product and Service Solutions (SPSS).

RESULTS AND DISCUSSION

Data Characteristics

In this study, a total of 570 drugs were evaluated for their suitability using the Dosing GAMA application. A total of 144 drugs were identified requiring dose adjustments. The result of the analysis using the application showed that the dosage was in accordance

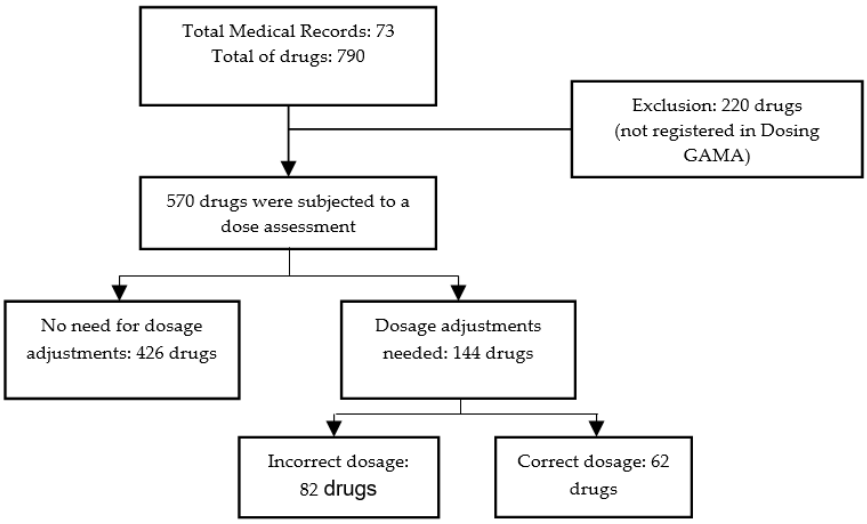

Figure 2. The number of research subjects on the evaluation of dose suitability using Dosing GAMA application

with the calculation results of 62 drugs (Figure).

Table I displays the data on the characteristics of inpatients with kidney disorders used in this study. These characteristic data include: sex (female and male), age (18-60 years and >60 years), treatment room (non-ICU and ICU), Creatinine Serum (SCr), Creatinine Clearance (CrCl), Glomerular Filtration Rate (eGFR) estimation criteria, and diagnosis. Creatinine clearance was calculated using the Cockcroft-Gault equation while eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

Based on gender characteristics, there were 51 RM (59.9%) from male gender. This is in line with the previous studies that patients with kidney problems were male[8,14,15]. In this study, 12 out of 20 patients who experienced CRF were male. According to the research conducted by Chang dkk. (2016), this could be related to the presence of risk factors that occur in male patients with CRF in the form of proteinuria, age, anemia, and uncontrolled blood pressure. However, in this study, further analysis related to these risk factors could not be carried out.

Characteristics of age in this study were categorized into elderly (>60 years) and non-elderly (18-60 years). This was based on the criteria for elderly patients issued by the Indonesian Ministry of Health where elderly patients are patients with an age above 60 years[17,18]. The average age for this study was 61.82 years, consisting of 56.2% (41 RM) with age criteria>60 years (Table I). This is in line with previous studies that patients with kidney problems were patients >60 years[14]. Elderly patients have a higher risk of experiencing decreased kidney function due to the decreased ability of organ function in the body[19,20], and have a health status that is dominated by multimorbidity, malnutrition, and organ failure[21].

Patients who are treated in the Intensive Care Unit (ICU) are patients with critical conditions and have multiple organ damage, one of them is the kidney. Organ dysfunction is a common condition in patients admitted to the ICU. The common organ dysfunctions or failure include pulmonary, cardiovascular, renal, hepatic, hematology, and central nervous system[22]. In this study, 74% of the data were obtained from non-ICU care rooms (internal medicine units) and 26% of the data

Table I. Characteristics of patients with impaired kidney function at RSA UGM

Characteristics	n	%	Average ± SD
Gender			
Female	22	30.1	
Male	51	69.9	
Age (years)			61.82 ± 14.842
18-60 years	32	43.8	
>60 years	41	56.2	
Ward			
Non-ICU	54	74	
ICU	19	26	
SCr (mg/dL)			3.39 ± 2.99
CrCl (mL/min)			25.49 ± 11.97
eGFR Criteria (mL/min/1.73m²)			
30-59	37	50.7	
15-29	18	24.7	
<15	18	24.7	
Diagnosis			
Diabetes Mellitus	48	65.8	
Hypertension	37	50.7	
Anemia	20	27.4	
Chronic Renal Failure	20	27.4	
Pneumonia	19	26	
Congestive heart failure (CHF)	18	24.7	
Urinary Tract Infection	14	19.2	
Acute renal failure (ARF)	13	17.8	
Hyperurisemia	11	15.1	
Ischemic heart disease (IHD)	10	13.7	
Hypokalemia, hyperkalemia	9	12.3	
Cerebrovascular Disease	8	11	
Hepatitis	6	8.2	
Hyperlipidemia	3	4.1	
Gallstones	3	4.1	
Cirrhosis of the liver	2	2.7	
Cirrhosis of the liver	1	1.4	

Note: SD = Standard Deviation; SCr = serum creatinine; ICU = Intensive Care; Unit; CrCl = Creatinine clearance (mL/min); n = number of patient medical records (73)

came from ICU care rooms. The number of ICU patients was recorded to be less than the non-ICU patients because the total number of patients admitted to the ICU was relatively less than non-ICU patients.

Creatinine is a product of muscle metabolism which is mainly eliminated by glomerular filtration[23], as the basis for determining the creatinine clearance value. The higher the creatinine value, the more serious the condition of decreased kidney function is. The serum creatinine mean value in this study was 3.39±2.99 mg/dL with an average creatinine clearance (CrCl) value of 25.49±11.97 mL/min. If calculated based on the GFR value, the majority of the samples were in

the range of 30-59 mL/min/m^2, which was 37 samples (50.7%).

As many as 27.4% patients were patients with CRF, acute renal failure (ARF) (17.8%), heart disease (42.5%), hyperuricemia (15.1%), infection (37%), and hypertension (50.7%), and diabetes mellitus (65.8%). The presence of diabetes mellitus, urinary tract infection disorders, cardiovasular disease, and ARF are risk factors for impaired kidney function. In addition, hypertension[16], cardiovascular disease, and ARF itself will also worsen kidney function conditions[24]. The patients with hypertension have a greater risk of developing End Stage Renal Disease (ESRD) and death than patients without hypertension[25].

Drug Dosage Assessment

Based on the results of the assessment of the Dosing GAMA application, there were 144 drugs (25.6%) that were deemed necessary to adjust the dose and 426 drugs (74.4%) were deemed not necessary to adjust the dose. A total of 82 drugs (56.9%) were assessed as having an inappropriate dose and 62 drugs (45.1%) were assessed as having an appropriate dose (Figure). These results indicate that the problem of drug dose adjustment in patients with kidney disorders is still found in clinical practice. The previous studies mentioned that the percentage of drug dose mismatch in patients with impaired kidney function was quite diverse, ranging from 13% to 81%. A study in Lebanon found 49% dose mismatch[9]. Several other countries such as Norway identified 45.5%[26]; China 15.18%[27]; India 81.11%[15]; Iran 54.4%[28]; Malaysia 53%[29]; Pakistan 58.2%[30]; and Indonesia (Jakarta) 13.5%[31]. The diversity of these data may be influenced by the role of doctors and clinical pharmacists in administering and evaluating therapeutic doses for patients with decreased renal function[32,33].

Table II describes the evaluation results of the dose suitability assessment using the Dosing GAMA application along with the type of drug that requires dosage adjustment in patients with kidney disorders.

In this study, it was found that, most of the drugs that required dose adjustment for patients with impaired renal function, included: cardiovascular drugs (26.4%); hyperuricemia (13.9%); antibiotics (11.8%); analgesics (11.8%); diuretics (11.1%); gastrointestinal drugs (8.3%). Types of drugs that were often given in inappropriate doses were cardiovascular drugs (31.7%), antibiotics (13.4%), analgesics (14.6%) and gastrointestinal drugs (14.5%). Similar to the results of previous studies, the drugs most frequently assessed for having Drug Related Problems (DRPs) in patients with impaired renal function are cardiovascular drugs, antimicrobials, antidiabetics, diuretics, allopurinol, ranitidine, metoclopramide[15,28–30,34]. The large number of uses of these drugs in this study was consistent with the diseases suffered by patients, such as cardiovascular disease, including hypertension (50.7%) and other cardiovascular diseases such as CHF and IHD (42.5%); diabetes mellitus (65.8%), hyperuricemia (15.1%), infections (37%), and liver diseases (9.6%).

Irrational use of drug doses is one of the factors that can affect the outcome of therapy, such as drug toxicity or ineffectiveness[3]. For example, in one case there was an increase in the serum creatinine level on the use of ketorolac 30mg/8 hours after the second day, from 1.56mg/dL to 2.37mg/dL. In this case, Dosing GAMA recommends giving ketorolac with a maximum dose of 60mg/day.

In Table III provides recommendations for drug doses based on the Dosing GAMA application. Dosing GAMA uses the Drug Information Handbook as a reference for dosage recommendation data.

Drugs for cardiovascular disease

Tranexamic acid is an antifibrinolytic. More than 95% of the drug will be excreted in the urine[35]. In this study, it was found that 13 times the injection was given at a dose of 500mg/8 hours and one oral distribution with a dose of 3x100mg. Dosing GAMA recommends injection of tranexamic acid at a dose of 10% of the normal dose in patients

Table II. Drug dose assessment based on Dosing GAMA

Drug classes	Drug names	Dose Appropriate		Dose Inappropriate		Total	
		n	%	n	%	n	%
Cardiovascular drugs	*Tranexamic Acid*	0	0	14	17.1	14	9.7
	Bisoprolol	7	11.3	0	0	7	4.7
	Candesartan	0	0	10	12.2	10	6.9
	Captopril	1	1.6	0	0	1	0.7
	Clonidine	0	0	1	1.2	1	0.7
	Digoxin	1	1.6	0	0	1	0.7
	Aspirin	3	4.8	1	1.2	4	2.8
Total		**12**	**19.4**	**26**	**31.7**	**38**	**26.4**
Antibiotics	*Ceftazidime*	0	0	4	4.9	4	2.8
	Cefixime	0	0	2	2.4	2	1.4
	Gentamycin	1	1.6	0	0	1	0.7
	Levofloxacin	0	0	5	6.1	5	3.5
	Meropenem	5	8.1	0	0	5	3.5
Total		**6**	**9.7**	**11**	**13.4**	**17**	**11.8**
Antidiabetics	*Glimepiride*	2	3.2	0	0	2	1.4
	Metformin	0	0	5	6.1	5	3.5
Total		**2**	**3.2**	**5**	**6.1**	**7**	**4.9**
Analgesics	*Ketorolac*	2	3.2	5	6.1	7	4.7
	Paracetamol	2	3.2	7	8.5	9	6.3
	Codeine	1	1.6	0	0	1	0.7
Total		**5**	**8.1**	**12**	**14.6**	**17**	**11.8**
Diuretics	*Mannitol*	0	0	2	2.4	2	1.4
	Furosemide	8	12.9	0	0	8	5.6
	Spironolactone	4	6.5	2	2.4	6	4.2
Total		**12**	**19.4**	**4**	**4.9**	**16**	**11.1**
Gastrointestinal drugs	*Ranitidine*	**0**	**0**	**12**	**14.6**	**12**	**8.3**
Antiemetic	*Metoclopramide*	**5**	**8.1**	**3**	**3.7**	**8**	**5.6**
Antigout	*Allopurinol*	**20**	**32.3**	**0**	**0**	**20**	**13.9**
Antihistamines	*Cetirizine*	**0**	**0**	**3**	**3.7**	**3**	**2.1**
Cholesterol drugs	*Fenofibrate*	**0**	**0**	**3**	**3.7**	**3**	**2.1**
Nervous system drugs	*Gabapentin*	**0**	**0**	**3**	**3.7**	**3**	**2.1**

Note: n = drugs amount; % = drugs amount percentage

with CrCl 10-50 mL/min or 10 mg/kg/dose every 48 hours and 15 mg/kg/dose every 48 hours for oral distribution.

The antihypertensives used in this study include: bisoprolol, candesartan, captopril, and clonidine. Angiotensin-converting enzyme (ACE) inhibitor and Angiotensin Receptor Blocker (ARB) are first-choice drugs for hypertension with type 1 or 2 diabetes mellitus, as well as proteinuria or early chronic kidney disease. This agent can reduce blood pressure and proteinuria with slow progression to the incidence of kidney disease, and is safe for the cardiovascular system. However, Dosing GAMA assesses that candesartan use is contraindicated in patients with CrCl <30 mL/min. Meanwhile, the drugs belonging to the hydrophilic beta blocker

(bisoprolol) and clonidine are considered safe for patients with impaired renal function, but still require dose adjustments[36].

Antidiabetics

Dosing GAMA does not recommend metformin for patients with serum creatinine levels > 1.5 mg/dL for male patients and > 1.4 mg/dL for female patients. As much as 90% of the drug will be excreted through the kidneys. In addition, in some cases metformin distribution will increase lactic acidosis. If necessary, it can be started at a low dose by monitoring the patient's response and tolerance. If there is an indication that the patient has sepsis, then the distribution of metformin should be stopped[36].

Antibiotics

Ceftazidime, cefixime, gentamycin, levofloxacin, and meropenem are antibiotics that are eliminated through the kidneys. Ceftazidime and cefixime are third generation of cephalosporin antibiotics. As much as 80-90% ceftazidime will be excreted in urine. In patients with decreased renal function, ceftazidime will have an extended half-life [35]. Dosing GAMA recommends giving ceftazidime every 12 hours for patients with CrCl values 30-50 mL/min and every 24 hours for patients with CrCl values 10-30 mL/min.

Cefixime has protein binding as much as 65% as well as an extended half-life in patients with impaired renal function up to 11.5 hours from normal conditions 3-4hours, so it is necessary to reduce the dose [35]. The recommended dose of cefixime by Dosing GAMA for patients with CrCl 21-60 mL/min or on hemodialysis is 75% of the standard dose.

Levofloxacin is a fluoroquinolone antibiotic. Levofloxacin will be excreted in urine (~87% in whole form). An extended half-life will occur in patients with CrCl values of 20-49mL/min (27 hours) and <20mL/min (35hours) [35]. Dosing GAMA recommends giving a dose of 750 mg/48 hours in patients with a CrCl value of 20-49 mL/min.

Analgesics

Paracetamol is a non-opioid analgesic which is considered safe for patients with impaired renal function. Dosing GAMA recommends giving a dose of 500mg every 6 hours for patients with a GFR of 10-50 mL/min/1.73m^2. While ketorolac is a Nonsteroidal anti-inflammatory drug (NSAID) analgesic with side effects such as acute renal failure, nephrotic syndrome with interstitial, and chronic renal failure with or without glomerulopathy, intertisial nephritis, and papillary necrosis. The risk of developing acute renal failure was 3 times higher in patients taking NSAID compared to those who did not [36]. Dosing GAMA recommends giving a dose of 30mg/12-24hours or 15 mg/6h in patients with a CrCl value of 10-50 mL/min.

Diuretics

Spironolakton is a potassium-sparing diuretic. Concomitant use with thiazide, furosemide or both may prevent hyperkalemia. Mannitol is an osmotic diuretics[35]. Dosing GAMA contraindicates mannitol use on patients with chronic renal impairment. Dosing GAMA recommends spironolactone given every 12-24 hours for patient with CrCl 10-50 mL/min.

Ranitidine

Ranitidine injection will be excreted through feces by 70% and its half-life is prolonged on patients with renal function impairment [35]. Dosing GAMA recommends 50 mg/18-24hours dosage of ranitidine for patients with CrCl <50mL/min. Inappropriate dosage found in this research is that ranitidine was injected every 12 hours, which is inappropriate in terms of frequency.

Metoclopramide

Metoclopramide is antiemetics drug from dopamine antagonist category. It will be excreted through urine by ~85%. Half-life of this drug depends on the prescribed dose, that is 5-6 hours for adult patients. The AUC will

Table III. Dosage recommendations based on Dosing GAMA

Drug Names	Amount (n)	Dosage given	Drug route	Dosing GAMA	
				Information	Recommendation
Tranexamic acid	13	500mg/8hours	Inj	CrCl 10-50 mL/min	10xkg Body Weight/ 48hours
	1	3x100mg	PO	CrCl 10-50 mL/min	15xkg Body Weight every 48hours
Candesartan	6	1x16mg	PO	CrCl<30mL/min	Contraindicated
	4	1x8mg	PO		
Clonidine	1	1x0.5mg	PO	CrCl <10 mL /min	2x0.05-0.1mg
Ceftazidime	1	1g/8hours	Inj	CrCl 30-50 mL/min	1g/12hours
	1	1g/8hours	Inj	CrCl 10-30 mL/min	1g/24hours
	2	1g/12hours	Inj		
Cefixime	2	2x200mg	PO	CrCl 21-60 mL/min or by hemodialysis	1x300mg or 2x150mg
Levofloxacin	4	750mg/ 24hours	Inj	CrCl 20-49 mL/min	750mg/48hours
Metformin	3	3x500mg	PO	SCr > 1.5 mg/dL in men, or > 1.4 mg/dL in women	Contraindicated
	1	1x500mg	PO		
	1	2x500mg	PO		
Ketorolac	5	30mg/8hours	Inj	GFR 10-20 mL/min/1.73m^2	30mg/12-24hours or 15mg/6hours
Paracetamol	7	3x500mg	PO	GFR 10-50 mL/min/1.73m^2	4x500mg
Mannitol	2	125mL/ 6hours	Inj	GFR <10 mL/min/1.73m^2	Contraindicated
Spironolactone	1	2x100 mg	PO	CrCl 10-50 mL/min	1-2x12.5-25mg
	1	1x100 mg	PO		
Ranitidine	9	25mg/ 12hours	Inj	CrCl <50mL/min	50 mg/18-24hours
	3	50mg/ 12hours	Inj		
Metoclopramide	3	10mg/8hours	Inj	CrCl < 40 mL/min	5mg/6-12hours
Fenofibrate	1	1x300mg	PO	GFR <30 mL/min/1.73 m^2	Contraindicated
	1	1x100mg	PO		
	1	1x150mg	PO		
Gabapentin	1	1x300mg	PO	CrCl> 30-59 mL/min	2x200mg
	1	2x100mg	PO		
	1	1x100mg	PO		
Cetirizine	3	1x10mg	PO	CrCl 11-31 mL/min	1x5mg

Note: Drug route = drug distribution route; Inj = Injection; PO = Per-Oral; CrCl = Creatinine Clearance; GFR = Glomerular Filtration Rate

Table IV. Demographic data effect on dose assessment

Parameter	Total Drug		*p-value*	Odds Ratio (CI 95%)
	Dose Inappropriate n (%)	Appropriate n (%)		
Gender				
Female	24 (66.7)	12 (33.3)	0.174	1.724 (0.783-3.797)
Male	58 (53.7)	50 (46.3)		
Age Category				
>60 years	53 (71.6)	21 (28.4)	0.000*	3.568 (1.783-7.142)
18-60 years	29 (41.4)	41 (58.6)		
CrCl				
<30 mL/min	58 (65.9)	30 (34.1)	0.006*	2.578 (1.295-5.133)
≥30 mL/min	24 (42.9)	32 (57.1)		
Total Drug				
>5 drugs	65 (56.0)	51 (43.9)	0.621	0.825 (0.355-1.915)
≤5 drugs	17 (60.7)	11 (39.3)		

Note: CrCl = creatinine clearance; *Chi-Square test with <0.05 significance; CI = Confidence Interval

increase on patients with renal function impairment, even as much as 2 times higher for patients under acute to chronic category[35]. Dosing GAMA recommends 50% normal dose of metoclopramide prescribed for patients with CrCl < 40 mL/min.

Cetirizine

Cetirizine has 93% protein binding with 8 hours half-life, and will be excreted through urine by 70% [35]. Dosing GAMA recommends 5mg/day dosage of cetirizine for patients with CrCl 11-31 mL/min.

Fenofibrate

Fenofibrate has ~99% protein binding. The half-life is 20 hours on patients with normal renal condition, and will be increased along with the functional impairment condition. 0% of this drug will be excreted through urine[35]. Dosing GAMA contraindicates the use of fenofibrate on patients with GFR <30 mL/min/1.73 m^2.

Gabapentin

Gabapentin is anticonvulsants or GABA analogue drug, has <3% protein binding with 5-7 hours half-life on patients with normal renal function. The half-life will increase along the renal function impairment severity [35]. Dosing GAMA recommends the following gabapentin dose: CrCl> 30-59 mL/min: 2x (200-700 mg); CrCl> 15-29 mL/min: 1x (200-700 mg); CrCl 15 mL/min: 1x (100-300 mg); and CrCl<15 mL/min: professionally decreased dose based on creatinine clearance value.

Dose Assessment Affecting Factors

The following is the result of factor analysis that is expected to affect the result of drug dose assessment.

Based on bivariate analysis (Table IV), it was found that there is no significant correlation between gender and total drug prescribed. However, there is significant correlation between age and creatinine clearance value to drug dose adjustment ($p<0.05$). Patients who are >60 years have 3.568 times higher risk of getting inappropriate drug dose prescription, while patients with CrCl value <30mL have 2.578 times higher risk of getting inappropriate drug dose prescription. This is in accordance with research by Breton dan rekan (2011)[7] and Saad (2019)[9] that

conclude elderly patients have higher risk of getting inappropriate drug dosage prescription. On the other hand, a research by Getachew dan rekan (2015) claimed that creatinine serum value has significant correlation with drug dosage adjustment prescribed to patient with renal impairment[8]. This is as elderly patients have higher risk of renal impairment due to the organ function impairment [19,20], following health status dominated by multimorbidity, malnutrition, and organ failure[21], that it causes increased drug dose and affects drug dosage adjustment.

From this research, it is concluded that by using Dosing GAMA application, clinical pharmacist in the hospital may have drug dose adjustment based on the patient's renal condition. Even so, this research have limitations. By using retrospective data, no real time intervention was possible on the drug prescription, the relatively small number of research sample, and also there were certain clinical consideration from the doctor and/or clinical pharmacist in the hospital that made different drug doses interpretation unavoidable. Furthermore, there are just limited drugs registered in Dosing GAMA. In this research, 19 drugs were not registered and in need of dose adjustment based on the renal impairment severity.

CONCLUSION

Dosing GAMA application is able to identify dose adjustment on 144 drugs from 570 drugs (25.6%) with 56.9% (82 drugs) are inappropriate dose. There is significant correlation (p<0.05) between age characteristic data (OR 3.568 (CI 95%: 1.783-7.142)) and CrCl value (OR 2.578 (CI 95%: 1.295-5.133)) to the therapy adjustment dose. There were problems found on the drug dose adjustment for renal impairment patient in clinical practice. Pharmacy Support System as in Dosing GAMA application could provide assistance to clinical pharmacy in identifying patient's drug use problem. Age and renal function characteristics of the renal impaired patients should actually be taken into consideration for pharmacist to assess dosage adjustment.

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