Evaluation of Renal Drug Dosing: Prescribing Information and Clinical Pharmacist Approaches

Thomas C. Dowling, Pharm.D., Ph.D., FCP, Gary R. Matzke, Pharm.D., FCCP, John E. Murphy, Pharm.D., FCCP, FASHP, and Gilbert J. Burckart, Pharm.D., FCCP, FCP

Study Objective. To characterize renal function parameters reported in United States Food and Drug Administration–approved prescribing information (package inserts), to compare dosage recommendations for patients with impaired renal function between prescribing information and tertiary drug dosing references, and to evaluate renal function quantification methods most commonly used by clinical pharmacists to develop dosage regimens.

Design. Retrospective analysis and Web-based survey.

Data Sources. Prescribing information for all new molecular entities (NMEs) approved from 1998–2007 in which dosing recommendations were proposed for patients with impaired renal function, drug monographs from four tertiary drug dosing references (Micromedex, Lexi-Comp, Epocrates Rx, and American Hospital Formulary Service [AHFS] Drug Information) for all identified NMEs, and a Web-based survey of 204 nephrology and critical care pharmacy practitioners.

Measurements and Main Results. A total of 44 NMEs included renal dosing recommendations in their prescribing information. For all 44 NMEs, prescribing information was reviewed to determine methods to quantify renal function, units of measure reported, and use of chronic kidney disease terminology. The most common index of renal function was creatinine clearance; the Cockcroft-Gault equation was specified in the prescribing information of 11 NMEs. Standardization for body weight was inconsistent, with prescribing information for four NMEs reporting renal function in ml/minute/1.73 m^2. The prescribing information or tertiary sources did not mention use of estimated glomerular filtration rate (eGFR) or the Modification of Diet in Renal Disease Study (MDRD) equation. Epocrates Rx provided the most abbreviated renal dosing information, whereas AHFS Drug Information was the most comprehensive, and Lexi-Comp includes a renal function calculator. Nearly all (86%) clinical pharmacists indicated that automated eGFR is reported at their institutions, although they do not use these predictions for dosing in patients with impaired renal function, and their approaches to renal function estimation varied widely.

Conclusion. Reporting of renal function methods and dosing recommendations for patients with impaired renal function requires standardization in order to ensure optimal dosing. Pharmacy clinicians do not substitute eGFR in place of creatinine clearance for renal dosing, which is consistent with current prescribing information. Studies are needed that will evaluate the validity of using eGFR to predict drug clearance and thereby generate dosage recommendations.

Key Words: new molecular entity, NME, drug dosing, drug safety, glomerular filtration rate, GFR, kidney function.

(Pharmacotherapy 2010;30(8):776–786)

The adjustment of drug dosing regimens for individuals with chronic kidney disease (CKD) or acute kidney injury (AKI) has been widely recognized as an essential aspect of individualized

pharmacotherapy. This approach to patient care management is now a part of the core curriculum of most doctor of pharmacy education programs, and a broad array of secondary and tertiary reference sources are available for clinicians to use as the basis for the initiation of such a program in their institution and/or practice. One of the challenges of getting the "right" dosage regimen is accurately determining or, in most cases, estimating the individual patient's renal function. Many renal function estimation approaches have been proposed, and the Cockcroft-Gault equation, which provides an estimate of creatinine clearance (Cl_{cr}), has gained the most widespread acceptance.[1] Recently, several equations to estimate renal function as glomerular filtration rate (eGFR) have emerged from a secondary analysis of the Modification of Diet in Renal Disease (MDRD) study.[2] The availability of these methods has stimulated assessments of the accuracy of the various methods for estimation of renal function (eGFR vs Cl_{cr}) in a broad array of patient populations. The automated reporting of eGFR, calculated from the four-variable MDRD equation, is now routinely provided by many hospital laboratories whenever a serum creatinine value is measured, as a tool to enhance the iden-tification and classification of individuals with CKD. This initiative coupled with the introduction of a new calibrated creatinine assay has led to uncertainty among practitioners as to which method of renal function assessment should be used as the foundation for individualizing dosage regimens.[3,4]

Assessment of renal function in the clinical setting is most often accomplished by estimating Cl_{cr}, which can be used as an index of the need for starting drug therapy at a reduced dosage or frequency or for altering a current dosage regimen; to determine a priori pharmacokinetic parameter estimates to facilitate the calculation of an individualized dosage regimen for drugs with a narrow therapeutic index; and to monitor renal function status in order to identify the early onset of nephrotoxicity. This is most important for drugs that are eliminated primarily by renal mechanisms or that are not monitored by using drug concentrations to guide dosing. For example, if the dofetilide dosage is not tailored for patients with CKD or AKI, their safety could be jeopardized since a strong relationship between elevated plasma concentrations and adverse outcomes has been noted, including QT-interval prolongation and ventricular arrhythmias.[5]

In an effort to improve the standardization and quality of renal dosing information provided by drug manufacturers in their drug labeling for new molecular entities (NMEs), the United States Food and Drug Administration (FDA) published its "Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling" (referred to as the Guidance in this article) in 1998.[6] The impact of this Guidance on the clarity, consistency, and quality of the labeling regarding drug dosing recommendations was assessed very early after its implementation, but a rigorous assessment remains to be conducted.[7] Furthermore, whether the relationship between the NME's pharmacokinetic parameters and clinically relevant renal function parameters such as measured or estimated Cl_{cr} or GFR has been adopted or incorporated into tertiary and Web-based reference sources has not been determined.

The objectives of this study were 3-fold: to characterize the renal function parameters used as foundational indexes to indicate the need for renal dosage adjustment provided in prescribing information for NMEs approved in the post-Guidance era (1998–2007), to tabulate the renal function parameters in four commonly used tertiary drug dosing references, and to evaluate the renal function quantification methods most commonly used by nephrology and critical care clinical pharmacists to develop individualized dosage regimens for patients with CKD or AKI.

Methods

Prescribing information (package inserts) for all

From the Department of Pharmacy Practice and Science, School of Pharmacy, University of Maryland, Baltimore, Maryland (Dr. Dowling); the Schools of Pharmacy and Medicine, Virginia Commonwealth University, Richmond, Virginia (Dr. Matzke); the Department of Pharmacy Practice and Science, Colleges of Pharmacy and Medicine, University of Arizona, Tucson, Arizona (Dr. Murphy); and the Office of Clinical Pharmacology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, Maryland (Dr. Burckart).

Presented in part at the annual meeting of the American College of Clinical Pharmacy, Louisville, Kentucky, October 18–22, 2008.

The comments in this article are those of the authors and do not represent the official position of the U.S. Food and Drug Administration.

Manuscript received September 24, 2009. Accepted pending revisions November 30, 2009. Accepted for publication in final form January 19, 2010.

For reprints, visit http://www.atypon-link.com/PPI/loi/phco. For questions or comments, contact Thomas C. Dowling, Pharm.D., Ph.D., FCP, Department of Pharmacy Practice and Science, School of Pharmacy, University of Maryland, 100 North Penn Street, AHB Room 540, Baltimore, MD 21201; e-mail: tdowling@rx.umaryland.edu.

NMEs approved by the FDA from June 1998–May 2007 was reviewed during the study period of May–August 2008. The most recent approved versions of the prescribing information, or full prescribing information, were downloaded directly from the respective innovator drug manufacturers' Web sites. Prescribing information that included a recommendation for renal dosage adjustment was reviewed to identify the following: renal function quantification method proposed as the index for dosage adjustment; the unit of measure for renal function quantification (e.g., ml/min, ml/min/1.73 m^2, ml/min/kg); the renal function severity categoric terms and the associated quantitative renal function values (e.g., 60–89 ml/min for mild impairment); and use of CKD classification and staging terminology.

The drug monographs of the NMEs for which drug dosage adjustments were recommended in their prescribing information, contained in four commonly used tertiary drug dosing references—Micromedex (DrugDex, Greenwood Village, CO), Lexi-Comp (Lexi-Drugs Online, Hudson, OH), Epocrates Rx (San Mateo, CA), and American Hospital Formulary Service (AHFS) Drug Information (American Society of Health-System Pharmacists, Inc., Bethesda, MD)—were reviewed in August 2009 to ascertain if the information they contained was consistent with the renal dosing information provided in the prescribing information.

Finally, a cross-sectional survey was conducted of members of the Nephrology and the Critical Care Practice and Research Networks of the American College of Clinical Pharmacy (ACCP) to ascertain the renal function indexes used by these practitioners for providing renal drug dosing individualization in clinical settings, and to determine if differences existed. The 7-item questionnaire was constructed and distributed from January–February 2009 by using a Web-based survey tool (www.SurveyMonkey.com). The construct of the survey and the scope of the data analysis plan were approved by the University of Maryland institutional review board. The questionnaire addressed the following: which, if any, of the MDRD equations[2] were used to estimate GFR; what method was most often used to estimate renal function for drug dosage adjustment; if they used any method other than the patient's actual body weight to estimate renal function in overweight patients when using the Cockcroft-Gault equation[1] to estimate Cl_{cr} or if they used the Salazar-Corcoran equation[8] in this patient population; and finally, what were the top 10 drugs in their practice setting for which they provided renal dosing recommendations. Survey responses were evaluated between the two practitioner groups (nephrology and critical care pharmacists) by using χ^2 analysis (SAS, version 9.1; SAS Institute Inc., Cary, NC). A p value of less than 0.05 was considered to indicate a statistically significant difference.

Table 1. List of the 44 New Molecular Entities Reviewed

Generic Name	NDA No.
Acamprosate calcium	021431
Adefovir dipivoxil	021449
Almotriptan malate	021001
Anakinra	103950 (BLA no.)
Apomorphine	021264
Bivalirudin	020873
Cefditoren pivoxil	021222
Daptomycin	021572
Desloratadine	021165
Dofetilide	020931
Duloxetine	021427
Emtricitabine	021500
Entecavir	021797
Ertapenem	021337
Exenatide	021773
Fondaparinux sodium	021345
Gadoversetamide	020937
Galantamine	021169
Gemifloxacin mesylate	021158
Ibandronate sodium	021455
Lanreotide	022074
levetiracetam	021035
Meloxicam	020938
Memantine	021487
Miglustat	021348
Oseltamivir phosphate	021087
Oxcarbazepine	021014
Paliperidone	021999
Peginterferon alfa-2a	103964 (BLA no.)
Peginterferon alfa-2b	03949 (BLA no.)
Pemetrexed disodium	021462
Pregabalin	021446
Rosuvastatin calcium	021366
Sitagliptin phosphate	021995
Solifenacin succinate	021518
Tadalafil	021368
Telbivudine	022011
Telithromycin	021144
Tenofovir disoproxil fumarate	021356
Tiotropium bromide monohydrate	021395
Trospium chloride	021595
Varenicline tartrate	021928
Voriconazole	021267
Zolendronic acid	021223

NDA = new drug application; BLA = biologics license application.

Results

Drug dosing recommendations for patients with CKD or AKI were identified in the Clinical

Table 2. Examples of Renal Function Reporting in the Prescribing Information

Review Criteria	New Molecular Entity	Terminology Used in Prescribing Information
Cl_{cr} range or renal function category not consistent with the Guidance[6]	Voriconazole[9]	Severe renal insufficiency (Cl_{cr} < 50 ml/min)…
	Galantamine[10]	Severe renal impairment (Cl_{cr} < 9 ml/min)…
	Meloxicam[11]	In patients with mild to moderate renal failure (Cl_{cr} > 15 ml/min)…
	Oxcarbazepine[12]	Impaired renal function (Cl_{cr} < 30 ml/min)
Semiquantitative index of renal function	Almotriptan[13]	Severe renal impairment
	Galantamine[10]	Moderately impaired renal function
	Lanreotide[14]	Moderate to severe renal impairment
	Desloratidine[15]	Renal impairment
Nonstandard units of renal function measure	Rosuvastatin[16]	ml/min/1.73 m^2
	Miglustat[17]	ml/min/1.73 m^2
	Cefditoren[18]	ml/min/1.73 m^2
	Ertapenem[19]	ml/min/1.73 m^2
	Gadoversetamide[20]	ml/min/1.73 m^2

Cl_{cr} = creatinine clearance.

Table 3. Examples of Ambivalent Dosing Information in Prescribing Information for Selected New Molecular Entities

Generic Name	Renal Dosing Information in Prescribing Information
Memantine[21]	"Adequate information in renal impairment is not available…" "Renal impairment will likely have higher exposure…" "Dose reduction in patients with moderate renal impairment should be considered…" "Avoid in severe renal impairment."
Ranolazine[22]	"In patients with varying degrees of renal impairment, ranolazine plasma levels increased up to 50%. The PK of ranolazine has not been assessed in patients on dialysis."[a]
Fondaparinux[23]	"…should be used with caution in patients with moderate renal impairment (creatinine clearance 30–50 ml/min)."
Exenatide[24]	"Byetta is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min)"
Meloxicam[11]	"There is no need for dose adjustment in patients with mild to moderate renal failure (Cl_{cr} >15 ml/min). Patients with severe renal insufficiency have not been adequately studied. The use of Mobic [brand name] in subjects with severe renal impairment is not recommended."
Miglustat[17]	"Cl/F is decreased by at least 70% in severe renal impairment, therefore use in severe renal impairment is not recommended."

PK = pharmacokinetics; Cl_{cr} = creatinine clearance; Cl/F = apparent clearance where F is bioavailability.
[a]In dose administration section, no renal dose recommendation is given.

Pharmacology (Special Populations), Precautions, and/or Dosage Administration sections of the most current prescribing information for 44 of the 251 NMEs approved by the FDA during 1998–2007 (Table 1). The remaining 207 NMEs contained no specific renal dosing recommendations. For 8 of these 44 NMEs, an altered dosage regimen was proposed; however, no quantifiable index of renal function was reported in the renal dose recommendation label language, or the renal function terminology and quantitative categories were inconsistent with those suggested in the Guidance (Table 2).[9–20]

The most common measure of renal function reported as the index to guide dosage adjustment in the prescribing information was Cl_{cr} (42 of 44 NMEs). The quantitative renal function characterizations of the descriptive categoric terminology information in the prescribing information was almost uniformly consistent with the definitions and ranges of renal function as recommended in the Guidance: mild (Cl_{cr} 50–80 ml/min), moderate (Cl_{cr} 30–50 ml/min), or severe (Cl_{cr} < 30 ml/min) renal impairment. In four NMEs, the renal function terminology was dissimilar to that suggested in the Guidance (Table 2). In six NMEs, a lack of adequate information on renal impairment resulted in recommendations to either avoid using the drug in patients with severe renal insufficiency (Cl_{cr} < 30 ml/min) or an ambiguous recommendation was provided (Table 3).[11, 17, 21–24]

Table 4. Comparison of Tertiary Reference Data for 11 New Molecular Entities with Cockcroft-Gault Equation Specified in Prescribing Information

Generic Name	Body Weight Used[a]	Epocrates Rx	Micromedex	Lexi-Comp	AHFS
Premetrexed[25]	Actual	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Daptomycin[26]	Actual	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Dofetilide[5]	Actual	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	CGE WNS
Adefovir[27]	Ideal or lean	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Tenofovir[28]	Ideal or lean	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Gemifloxacin[29]	WNS	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Zoledronic acid[30]	WNS	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Levetiracetam[31]	WNS	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	CGE WNS
Pregabalin[32]	WNS	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS
Memantine[21]	WNS	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	CGE WNS
Sitaglitpin[33]	WNS	Cl_{cr} MNS	Cl_{cr} MNS	Cl_{cr} WEC	Cl_{cr} MNS

AHFS = American Hospital Formulary Service Drug Information; Cl_{cr} MNS = creatinine clearance determination method not specified; Cl_{cr} WEC = creatinine clearance determination method not specified, but Web-enabled calculator was provided; CGE = Cockcroft-Gault equation; WNS = weight not specified.

[a]In the Cockcroft-Gault equation in the prescribing information.

In the prescribing information for most NMEs, there was no indication if the clinician should use a measured or estimated Cl_{cr} to guide the selection of drug dosage. The Cockcroft-Gault equation for estimation of Cl_{cr} was specifically mentioned in the most current prescribing information of only 11 NMEs (Table 4).[5, 21, 25–33] Specific recommendations regarding the patient weight value that should be used in the estimation of Cl_{cr} were stated in the prescribing information of just five of these NMEs: actual body weight (three NMEs) and lean or ideal body weight (two NMEs). The use of new descriptors of renal function, such as CKD, eGFR, or MDRD, was not reported in the prescribing information of any NME, and the most commonly used units of measure for Cl_{cr} were ml/min (34 of 39 NMEs) and ml/min/1.73 m^2 (5 of 39 NMEs).

The Epocrates Rx drug monographs provided the most limited and abbreviated renal dosing information of the four tertiary reference sources. Fifteen deviations from prescribing information regarding renal function index of choice were noted, with the most common being the omission of units of renal function measurement. For example, the dosage recommendations for ertapenem and adefovir are given as "Cl_{cr} < 30: 500 mg qd," and "Cl_{cr} 30–49: give q48h," respectively. In all cases, details regarding Cl_{cr} estimation or determination methods were omitted compared with the prescribing information (Table 4). The Lexi-Comp resource did not state a specific method of estimating Cl_{cr} for any NME; however, the individual drug monographs included a "calculations" section that was linked to an interactive Cl_{cr} calculator. The calculator provided the user with an option to calculate Cl_{cr} by using either the Cockcroft-Gault equation (input actual body weight, yields Cl_{cr} in ml/min) or the Jelliffe equation[34] (no weight input variable, yields Cl_{cr} in ml/min/1.73 m^2).

The Micromedex and AHFS references provided dosage recommendations that were verbatim from the prescribing information in 41 of 44 NMEs, with the Cockcroft-Gault equation mentioned in some but not all cases. For Micromedex, deviations were related either to omissions or additional information provided from primary literature recommendations. For example, additional text in the Micromedex meloxicam monograph provided a dosing recommendation of 7.5 mg/day for patients with end-stage renal failure, whereas the prescribing information indicates that dosing in end-stage renal failure is not recommended.[11] This is likely the result of the rapid incorporation of new postapproval data into the Micromedex database and identifies another ongoing problem related to the failure of drug manufacturers to routinely update their prescribing information when new information becomes available.

Results of the survey of clinical pharmacist members of the Critical Care and the Nephrology Practice Research Networks of the ACCP are shown in Tables 5 and 6. The MDRD equation was used by nephrology pharmacy practitioners most frequently in patients with impaired renal function with a GFR less than 60 ml/min/1.73 m^2, whereas most of the critical care pharmacy practitioners never used the MDRD equation. Both groups used the Cockcroft-Gault equation in more than 90% of the patients for whom they

Table 5. Results of Pharmacist Renal Dosing Survey

Questionnaire Item	No. (%) of Respondents: Nephrology Pharmacists (n=55)	No. (%) of Respondents: Critical Care Pharmacists (n=149)	p Value
1. In what situations do you use the MDRD to calculate eGFR?			
All patients with CKD	8 (14.5)	6 (4.0)	<0.05
Only CKD patients with GFR < 60 ml/min/1.73 m^2	29 (52.7)	14 (9.4)	<0.001
I never use MDRD equation	12 (21.8)	115 (77.2)	<0.001
Other	5 (9.1)	14 (9.4)	NS
2. Which version of the MDRD equation do you use? Check all that apply.			
4-variable with IDMS-traceable assay	23 (41.8)	10 (6.7)	<0.001
4-variable without IDMS calibration	16 (29.1)	26 (17.4)	NS
6-variable	3 (5.5)	8 (5.4)	NS
Other	14 (25.5)	110 (73.8)	<0.001
3. Does your institution provide automated eGFR reporting?			
Yes	51 (92.7)	125 (83.9)	NS
No	4 (7.3)	24 (16.1)	NS
4. Which equation do you MOST often use to modify drug doses in renal patients?			
Cockcroft-Gault	53 (96.4)	141 (94.6)	NS
MDRD	0 (0)	0 (0)	NS
Other	2 (3.6)	8 (5.4)	NS
5. When using Cockcroft-Gault equation, which body weight do you use?			
Actual body weight all the time	1 (1.8)	1 (0.7)	NS
Ideal body weight all the time	15 (27.3)	29 (19.5)	NS
Some other body weight in overweight patients (i.e., adjusted body weight)	9 (16.4)	38 (25.5)	NS
Combination of above, depending on level of obesity	28 (50.9)	68 (45.6)	NS
I use the Salazar-Corcoran equation[8] in overweight patients	2 (3.6)	11 (7.4)	NS
6. Approximately how many of your patients undergo "measured" Cl_{cr} determinations?			
Approximately 1 patient/wk	10 (18.2)	23 (15.4)	NS
Approximately 1 patient/mo	20 (36.4)	57 (38.3)	NS
Approximately 1patient/yr	14 (25.5)	42 (28.2)	NS
Never	11 (20.0)	27 (18.1)	NS

MDRD = Modification of Diet in Renal Disease Study equation; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; NS = not statistically significant; IDMS = isotope dilution mass spectrometry; Cl_{cr} = creatinine clearance.

planned to modify a drug dosage regimen. A variety of different patient weight adjustments were reported to be used with the Cockcroft-Gault equation when patients were overweight or obese; however, neither pharmacy group used the Salazar-Corcoran equation for overweight patients more than 10% of the time. The Cl_{cr} was reported by both pharmacy groups to be determined by urine collection (measured Cl_{cr}) very infrequently, with 45% reporting never or at most one patient/year. Antibiotics were the predominant agents listed in the top drugs for which the pharmacists provided renal dosage adjustments in their practice sites, with ertapenem, voriconazole, and daptomycin being the only NMEs that ranked in the top 20 (Table 6). Vancomycin and the aminoglycosides (gentamicin and tobramycin) were in the top five for both practitioner groups.

Discussion

Drug dosage modification based on degree of renal insufficiency has been a standard of practice in many acute and ambulatory care settings for over 3 decades.[35–40] The goals of these programs are to maximize therapeutic outcomes, minimize drug toxicity, and reduce health care costs associated with drug administration, adverse events, and hospitalizations. The clarity of dosage adjustment recommendations provided in the prescribing information is especially important for drugs that undergo extensive renal elimination and those for which therapeutic drug monitoring is not routinely performed. In the clinical setting, the first critical step is to accurately quantify a patient's renal function by using a method that is consistent with the clinical pharmacokinetic trial data for that drug, which was submitted as part of that drug's FDA

Table 6. Pharmacist Survey Item 7: Rank Order of Top 10 Drugs for Which Renal Dosage Adjustments Were Recommended by Clinical Pharmacists

Rank	Drug	No. (%) of Critical Care Pharmacists (n=149)	Drug	No. (%) of Nephrology Pharmacists (n=55)
1	Piperacillin-tazobactam	141 (94.6)	Vancomycin	42 (76.4)
2	Vancomycin	126 (84.6)	Piperacillin-tazobactam	37 (67.3)
3	Ciprofloxacin, levofloxacin	125 (83.9)	Gentamicin, tobramycin	34 (61.8)
4	Gentamicin, tobramycin	124 (83.2)	Enoxaparin	29 (52.7)
5	Imipenem, meropenem, doripenem, ertapenem[a]	115 (77.2)	Imipenem, meropemen[a]	26 (47.3)
6	Enoxaparin	95 (63.8)	Ciprofloxacin	22 (40.0)
7	Cefepime	70 (47.0)	Gabapentin	17 (30.9)
8	Famotidine	56 (37.6)	Ganciclovir, valganciclovir	16 (29.1)
9	Fluconazole, voriconazole[b]	45 (30.2)	Cefepime	14 (25.5)
10	Ampicillin-sulbactam	31 (20.8)	Levofloxacin	14 (25.5)
11	Cefazolin	31 (20.8)	Acyclovir	12 (21.8)
12	Metoclopramide	29 (19.5)	Famotidine	12 (21.8)
13	Acyclovir	26 (17.4)	Cefazolin	11 (20.0)
14	Co-trimoxazole	24 (16.1)	Fluconazole	11 (20.0)
15	Ranitidine	24 (16.1)	Ampicillin-sulbactam	10 (18.2)
16	Ceftazidime	20 (13.4)	Digoxin	10 (18.2)
17	Digoxin	19 (12.8)	Allopurinol	9 (16.4)
18	Amikacin	16 (10.7)	Ceftazidime	8 (14.5)
19	Gabapentin	14 (9.4)	Daptomycin[a]	8 (14.5)
20	Allopurinol	13 (8.7)	Co-trimoxazole	7 (12.7)

[a]Includes a new molecular entity identified in the prescribing information review.

approval documentation.

The most common index of renal function reported by drug manufacturers in prescribing information for drug dosing in patients with impaired renal function was Cl_{cr}. The CKD staging criteria, which are based on an MDRD-calculated GFR value, were not mentioned in the prescribing information of any of the 44 NMEs. However, the widespread availability of the automated eGFR value in acute care settings (reportedly used in > 85% of institutions represented in our pharmacist survey), as well as recent recommendations by the National Kidney Disease Education Program,[41] raises concern that once generated, this renal function estimate could be used beyond its intended purpose of categorizing patients into CKD risk categories.[2]

Use of eGFR or other alternate approaches to quantify renal function that are dissimilar to the methods provided in the prescribing information could result in marked variation in the calculated dosage regimen. Recent studies have consistently reported that the four-variable MDRD-derived eGFR overestimates Cl_{cr} by up to 40% compared with the Cockcroft-Gault equation in patients with a GFR less than 60 ml/min/1.73 m^2 and that the use of eGFR for drug dosing has resulted in up to 50% higher prescribed doses of digoxin, amantadine, and cephalosporins.[42–45] An overestimation of renal function by 20% would lead to a 20% increase in dose, higher drug concentrations, and thereby an increased risk of adverse events and drug-related problems. Although the clinical and economic implications of these dosing errors are unknown, the consequences would be most significant for drugs with a narrow therapeutic index and for drugs requiring a priori estimation of pharmacokinetic parameters that have been traditionally based on Cl_{cr}, including digoxin, aminoglycosides, and vancomycin. Based on these concerns, many experts in the field of pharmacotherapy have cautioned against using alternate methods of renal function assessment outside of those reported in the prescribing information.[3, 46, 47]

Few studies have reported dose calculations based on eGFR that show agreement with dose calculations that used directly measured GFR. For example, eGFR was reportedly more accurate than Cl_{cr} for calculating the carboplatin dose when compared with measured GFR.[48] These findings are not surprising since eGFR equations are derived from iothalamate-measured GFR. A recent study reported that renal dosage adjustments based on eGFR values provided similar doses for selected drugs when compared with the

Cockcroft-Gault equation.[49] However, it is important to note that the renal function index used to calculate the "gold standard drug dose" against which both the eGFR and Cockcroft-Gault Cl_{cr} groups were compared was measured GFR. Measured GFR is not mentioned in the FDA Guidance recommendations, was not used in the drug manufacturer pharmacokinetic studies in patients with impaired renal function in the 44 NMEs we reviewed, and is rarely available to practicing clinicians. In addition, the approach used by these researchers to determine drug dosage based on eGFR involved correction based on body surface area (BSA) to yield units in ml/minute instead of ml/minute/1.73 m^2; this approach has not been previously used in CKD staging, nor is it the value so frequently reported by clinical laboratories.

Another concern with automated eGFR reporting is that many clinicians are unaware of the version of the MDRD equation or the isotope dilution mass spectrometry creatinine assay calibration method that is used at their institution. It is also apparent that physicians find it difficult to interpret the automated eGFR in the clinical setting and its role in patient care.[50] We have shown that the use of eGFR for the development of renal dosing information of NMEs is currently rare, and further research may ultimately suggest that it is superior to Cl_{cr} in predicting total drug clearance. Until data are available that fully characterize the relationship between renal dosage adjustment approaches and therapeutic outcomes, particularly for those drugs that do not undergo traditional therapeutic drug monitoring, this approach cannot be recommended. The common availability of eGFR suggests that its use in drug development and clinical practice must be evaluated.

The lack of clarity regarding the renal function index of choice for the renal drug dosage adjustment recommendations in the two tertiary resources that are most readily available to practicing clinicians and students is disconcerting. Approximately 250,000 physicians and 40,000 pharmacists are actively using Epocrates Rx software on mobile communication devices (personal communication, Erica Morgenstern, November 30, 2009). A recent survey revealed that medical students are 4 times more likely to consult a mobile reference for a clinical question than to ask their attending physician.[51] This could be due to intimidation or simply the inability to find someone to ask. Unfortunately, nearly 90% of students surveyed view the information available through mobile or online drug and disease references, such as Epocrates Rx, as highly credible, second only to medical journals. The availability and convenience, however, should not imply quality and may in fact (based on our data and that previously reported[52]) suggest a need for standardization of "trusted" resources.

The Cl_{cr} is the gold standard renal function index reported in prescribing information. The specific details regarding use of measured versus estimated Cl_{cr} is, however, rarely specified in the prescribing information, nor is the method for estimation reported. This may lead to potential errors in interpretation of renal dosage adjustments by health care providers. Methods used by clinicians that differ from the approaches used to create dosing guidelines for patients with impaired renal function increase the risk that a less than optimal dosage regimen might be implemented. Weight-based modifications of the Cockcroft-Gault equation are commonly reported in the literature.[53, 54] They are often used in clinical settings for overweight patients even though these approaches are not clearly specified in the prescribing information or in the pharmacokinetic studies of NMEs in patients with impaired renal function. This is likely because during drug development, obese individuals are most often excluded from pharmacokinetic studies or studies in patients with impaired renal function.

The results of our pharmacist survey indicate that most pharmacists use the Cockcroft-Gault equation to estimate renal function for renal drug dosage adjustments, and they apply a weight adjustment of the Cockcroft-Gault equation for overweight patients. The prescribing information for only a few NMEs recommend using a weight-based adjustment for the Cockcroft-Gault equation. Rigorous evaluation of these approaches is lacking, and the relationship between Cl_{cr} calculated by these approaches and either drug pharmacokinetic parameters or drug therapy outcomes is yet to be defined. The availability of renal function calculators in tertiary sources such as Lexi-Comp may minimize calculation errors. However, the user is still required to make a choice between the Cockcroft-Gault equation (using actual body weight only) and the Jelliffe equation (no body weight required), which introduces additional variation in the renal function estimate. Because dosing guidelines for patients with impaired renal function in the prescribing information do not clearly provide guidance on this issue, there could be marked interclinician variation in a

given patient's drug dosage regimen.

The units of measure reported for Cl_{cr} estimations in tertiary reference sources were often omitted and the recommended patient weight used to estimate Cl_{cr} was often not described, leading to controversy among practitioners. We identified five NMEs for which the prescribing information indicated that a BSA correction would have to be applied to the Cockcroft-Gault–estimated Cl_{cr} values to yield results in the desired units of measure of ml/minute/1.73 m^2 (Table 2). Another problem with the BSA-corrected approach is that there is no universally agreed-upon method to calculate it among investigators or regulators. Because of this, including BSA in renal drug dosing is likely to introduce a magnitude of variability in dosage calculations and recommendations. Since BSA is not often calculated in clinical settings, the best practice would be for drug manufacturers to avoid reporting Cl_{cr} by using this unit of measure.

When dosing recommendations are provided for patients with impaired renal function, they are often based on one or more small, underpowered, unpublished pharmacokinetic studies that may only be referenced in review articles as "data on file" or not available at all. This can lead to ambiguous or problematic dosage regimen recommendations for patients with severe renal insufficiency, such as "insufficient data available" to make a dosing recommendation, as noted in about 10% of the NMEs (Table 3). Other noted shortcomings of renal drug dosing studies include lack of representative populations that would be treated with the drug (i.e., populations based on obesity, age, sex, race-ethnicity), incomplete understanding of which pharmacokinetic parameters (e.g., area under the concentration-time curve, average steady-state concentration, maximum concentration, minimum concentration) are important to match for renally impaired patients compared with those with normal renal function, and lack of pharmacodynamic outcomes to ensure adequate response and avoidance of adverse effects when renal drug dosing recommendations are applied. Publication of pharmacokinetic studies and studies in patients with impaired renal function and availability of the raw pharmacokinetic data in the public domain can provide further information about critical study methods, including the method of estimating renal function. For example, the prescribing information often suggests a renal dosage adjustment based on Cl_{cr}, whereas the pharmacokinetic studies or studies in patients with impaired renal function might report that patients were stratified in the trial based on estimated Cl_{cr} by using the Cockcroft-Gault equation with no weight index specified (e.g., telbivudine) or based on a 24-hour urine collection (solifenacin).[55, 56] In such cases, the practitioner has to make a clinical judgment regarding which Cl_{cr} estimation method they will use for dosage adjustment purposes; this most often leads to use of some form of the Cockcroft-Gault equation and involves a weight-based Cockcroft-Gault equation. Having these critical aspects of the pharmacokinetic studies and studies in patients with impaired renal function included in the medical or clinical pharmacology reviews that are available on the FDA Center for Drug Evaluation and Research (CDER) Web site or provided as active Web links within the Web-residing prescribing information would be helpful. A best practice would be to conduct pharmacokinetic studies and studies in patients with impaired renal function by using Cl_{cr} from an accurately timed 24-hour Cl_{cr} or Cockcroft-Gault equation with a specified weight index to stratify patients into renal function categories, with poststudy analysis of the relationship between the critical pharmacokinetic parameters and variants of the Cockcroft-Gault and eGFR equations. This approach would provide maximum transparency and avoid major assumptions associated with renal function estimation methods. Appendix 1 provides a list of our best practice recommendations.

The prescribing information provided to clinical practitioners is the result of a negotiation between the FDA and the drug sponsor. The FDA CDER review teams are composed of physicians, clinical pharmacologists, biostatisticians, and others, who make recommendations for drug labeling. The February 2009 draft guidance on labeling for human prescription drugs and biologics[57] identifies where renal dosing guidelines should be provided but does not provide the detail to the extent that we suggest. The FDA's 2008 preliminary concept paper[58] updates the 1998 document[6] but has made very few changes in the recommended labeling section. As the concept paper receives comments and evolves into an official guidance, an investigation such as presented here should help to inform the process.

Conclusion

Reporting of renal function estimation methods

and dosing recommendations for patients with impaired renal function would benefit from standardization not only in the study conduction process but also the language of the labeling that appears in official prescribing information and secondary and tertiary sources. This would enhance the potential for optimal dosing of drugs that are excreted primarily unchanged by the kidneys. Substitution of alternate methods of renal function estimation, such as eGFR, in place of Cl_{cr}, for renal dosing is not supported by the results of this study, which revealed that in the clinical setting and drug development arenas Cl_{cr} is by far considered the renal function index of choice. Widespread adoption of eGFR for renal dosing will require either new studies for each drug or a secondary analysis of the original data from the previous investigations conducted of these NMEs.

Acknowledgment

The authors thank Danil Podolskiy, Pharm.D., and Ted Kim, Pharm.D., for their assistance with data acquisition.

References

1. **Cockcroft DW, Gault MH**. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
2. **Levey AS, Coresh J, Greene T, et al**. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54.
3. **Spruill WJ, Wade WE, Cobb HH**. Estimating glomerular filtration rate with a modification of diet in renal disease equation: implications for pharmacy. Am J Health Syst Pharm 2007;64:652–60.
4. **Mathew TH, Johnson DW, Jones GR**. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. Med J Aust 2007;187:459–63.
5. **Pfizer Inc**. Tikosyn (dofetilide) package insert. New York, NY; 2006.
6. **U.S. Food and Drug Administration**. Guidance for industry: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). May 1998. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072127.pdf. Accessed June 11, 2009.
7. **Ibrahim S, Honig P, Huang SM, et al**. Clinical pharmacology studies in patients with renal impairment: past experience and regulatory perspectives. J Clin Pharmacol 2000;40:31–8.
8. **Salazar DE, Corcoran GB**. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med 1988;84:1053–60.
9. **Pfizer Inc**. VFEND (voriconazole) package insert. New York, NY; 2008.
10. **Ortho-McNeil-Janssen Pharmaceuticals, Inc**. Razadyne (galantamine) package insert. Titusville, NJ; 2008.
11. **Boehringer Ingelheim Pharmaceuticals, Inc**. Mobic (meloxicam) package insert. Ridgefield, CT; 2008.
12. **Novartis Pharmaceuticals Corp**. Trileptal (oxcarbazepine) package insert. East Hanover, NJ; 2007.
13. **Ortho-McNeil Pharmaceuticals**. Axert (almotriptan) package insert. Raritan, NJ; 2007.
14. **Tercica, Inc**. Somatuline (lanreotide) package insert. Brisbane, CA; 2007.
15. **Schering Corporation**. Clarinex (desloratidine) package insert. Kenilworth, NJ; 2007.
16. **AstraZeneca Pharmaceuticals**. Crestor (rosuvastatin) package insert. Wilmington, DE; 2009.
17. **Acetlion Pharmaceuticals**. Zavesca (miglustat) package insert. San Francisco, CA; 2008.
18. **Cornerstone BioPharma Inc**. Spectracef (cefditoren) package insert. Cary, NC; 2007.
19. **Merck & Co, Inc**. Invanz (ertapenem) package insert. Whitehouse Station, NJ; 2008.
20. **Mallincrodt, Inc**. OptiMARK (gadoversetaminde) package insert. St. Louis, MO; 2009.
21. **Forest Pharmaceuticals, Inc**. Namenda (memantine) package insert. St. Louis, MO; 2007.
22. **CV Therapeutics, Inc**. Ranexa (ranolazine) package insert. Palo Alto, CA; 2009.
23. **GlaxoSmithKline**. Arixtra (fondaparinux) package insert. Research Triangle Park, NC; 2008.
24. **Amylin Pharmaceuticals, Inc**. Byetta (exenatide) package insert. San Diego, CA; 2008.
25. **Eli Lilly & Co**. Alimta (pemetrexed) package insert. Indianapolis, IN; 2009.
26. **Cubist Pharmaceuticals, Inc**. Cubicin (daptomycin) package insert. Lexington, MA; 2008.
27. **Gilead Sciences, Inc**. Hepsera (adefovir) package insert. Foster City, CA; 2008.
28. **Gilead Sciences, Inc**. Viread (tenofovir) package insert. Foster City, CA; 2008.
29. **Oscient Pharmaceuticals**. Factive (gemifloxacin) package insert. Waltham, MA; 2008.
30. **Novartis Pharmaceuticals**. Zometa (zoledronic acid) package insert. East Hanover, NJ; 2008.
31. **UCB, Inc**. Keppra (levetiracetam) package insert. Smyrna, GA; 2008.
32. **Pfizer, Inc**. Lyrica (pregabalin) package insert. New York, NY; 2009.
33. **Merck & Co., Inc**. Januvia (sitagliptin) package insert. Whitehouse Station, NJ; 2007.
34. **Jelliffe RW**. Creatinine clearance: bedside estimate [letter]. Ann Intern Med 1973;79:604.
35. **Berbatis CG, Eckert GM, Neale FG, Rothwell JP**. Quality assurance of drug therapy in hospitals: patient serum creatinine values used by ward pharmacists in checking dosage regimens. Med J Aust 1979;1:46–7.
36. **Libiszewski D**. The development of a drug dosage adjustment service for patients with renal impairment. J Clin Hosp Pharm 1981;6:39–49.
37. **Peterson JP, Colucci VJ, Schiff SE**. Using serum creatinine concentrations to screen for inappropriate dosage of renally eliminated drugs. Am J Hosp Pharm 1991;48:1962–4.
38. **Golightly LK, O'Fallon CL, Moran WD, Sorocki AH**. Pharmacist monitoring of drug therapy in patients with abnormal serum creatinine levels. Hosp Pharm 1993;28:725–7.
39. **McMullin ST, Reichley RM, Kahn MG, et al**. Automated system for identifying potential dosage problems at a large university hospital. Am J Health Syst Pharm 1997;54:545–9.
40. **Gupta SR, Wojtynek JE, Walton SM, et al**. Monitoring of pharmacy staffing, workload, and productivity in community hospitals. Am J Health Syst Pharm 2006;63:1728–34.
41. **National Kidney Disease Education Program**. CKD and drug dosing: information for providers. Available from http://www.nkdep.nih.gov/professionals/drug-dosing-information.htm. Accessed October 1, 2009.
42. **Wargo KA, Eiland EH, Hamm W, et al**. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for antimicrobial dosage adjustments. Ann Pharmacother 2006;40:1248–53.
43. **Gill J, Malyuk R, Djurdjev O, Levin A**. Use of GFR equations

to adjust drug doses in an elderly multi-ethnic group: a cautionary tale. Nephrol Dial Transplant 2007;22:2894–9.
44. **Golik MV, Lawrence KR**. Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: Cockcroft-Gault and modification of diet in renal disease. Pharmacotherapy 2008;28:1125–32.
45. **Hermsen ED, Maiefski M, Florescu MC, et al**. Comparison of the modification of diet in renal disease and Cockcroft-Gault equations for dosing antimicrobials. Pharmacotherapy 2009;29:649–55.
46. **Wolowich WR, Raymo L, Rodriguez JC**. Problems with the use of the modified diet in renal disease formula to estimate renal function. Pharmacotherapy 2005;25:1283–5.
47. **Bauer L**. Creatinine clearance versus glomerular filtration rate for the use of renal drug dosing in patients with kidney dysfunction. Pharmacotherapy 2005;25:1286–7.
48. **de Lemos ML, Hsieh T, Hamata L, et al**. Evaluation of predictive formulae for glomerular filtration rate for carboplatin dosing in gynecological malignancies. Gynecol Oncol 2006;103:1063–9.
49. **Stevens LA, Nolin TD, Richardson MM, et al**. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. Am J Kidney Dis 2009;54:33–42
50. **Freedberg DE**. To eGFR or not to eGFR: here is an intern's answer. Kidney Int 2009;76:129–30.
51. **Snyder M**. Medical students want you to know. The health blog. Available from http://www.thehealthcareblog.com/the_health_care_blog/2009/09/medical-students-want-you-to-know-.html. Accessed September 16, 2009.
52. **Vidal L, Shavit M, Fraser A, et al**. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function [online exclusive article]. BMJ 2005;331:263. Available from http://www.bmj.com/cgi/content/full/331/7511/263?view=long&pmid=15905228.
53. **Demirovic JA, Pai AB, Pai MP**. Estimation of creatinine clearance in morbidly obese patients. Am J Health Syst Pharm 2009;66:642–8.
54. **Verhave JC, Balje-Volkers CP, Hillege HL, De Zeeuw D, De Jong PE**. The reliability of different formulae to predict creatinine clearance. J Int Med 2003;253:563–73.
55. **Zhou XJ, Swan S, Smith WB, et al**. Pharmacokinetics of telbivudine in subjects with various degrees of renal impairment. Antimicrob Agents Chemother 2007;51:4231–5.
56. **Smulders RA, Smith NN, Krauwinkel WJ, Hoon TJ**. Pharmacokinetics, safety, and tolerability of solifenacin in patients with renal insufficiency. J Pharmacol Sci 2007;103:67–74.
57. **U.S. Food and Drug Administration**. Guidance for industry: clinical pharmacology section of labeling for human prescription drug and biological products—content and format. Draft guidance, February 2009. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf. Accessed June 11, 2009.
58. **U.S. Food and Drug Administration**. Backgrounder for the advisory committee for pharmaceutical science and clinical pharmacology meeting, March 18–19, 2008: preliminary concept paper: pharmacokinetics in patients with impaired renal function—study design, data analysis, and impact on dosing and labeling, pp. 57–73. Available from http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008–4351b1–01–FDA.pdf. Accessed June 11, 2009.

Appendix 1. Authors' Best Practice Recommendations

1. Drug manufacturers should conduct pharmacokinetic studies and studies in patients with impaired renal function by using accurately timed 24-hour creatinine clearance (Cl_{cr}), or the estimated Cockcroft-Gault equation with weight index specified to stratify patients into renal function categories, with poststudy analysis of performance of alternate methods such as estimated glomerular filtration rate (eGFR) equations.
2. Drug manufacturers should avoid reporting Cl_{cr} in terms of body surface area (ml/min/1.73 m^2).
3. Drug manufacturers should avoid reporting GFR or eGFR in prescribing information for new molecular entities until results from pharmacokinetic studies are confirmed.
4. Drug manufacturers should publish pharmacokinetic studies and studies in patients with impaired renal function in the scientific literature as soon as possible and provide direct links to these publications by using Internet-assisted methods.
5. Prescribing information should include specific details regarding the renal index used to categorize patients in pharmacokinetic studies.
6. Clinical practitioners should review prescribing information or primary literature for the appropriate renal function index to be used for renal dosing.
7. Editors of tertiary reference sources should ensure accurate translation of renal dosing information from prescribing information.
8. Clinical trials should be designed to quantify the relationship between newly proposed renal function equations and variants (i.e., Modification of Diet in Renal Disease Study [MDRD] equation, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation, and weight-based modifications of the Cockcroft-Gault equation) and drug pharmacokinetic parameters, and the necessity for dosage adjustments to ensure optimal patient outcomes.