

Approaches to Drug Dosing in Renal Dysfunction

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Objectives

- Evaluate evidence for the value in adjusting doses of renally excreted drugs in patients with diminished renal function.
- Discuss approaches used (historical perspectives).
- Consider issues related to prediction.

Is There a Need?

- How drugs are eliminated and excreted are well known
- FDA requires dosing adjustment guidelines for drugs excreted renally if they are to be used in patients with diminished renal function
- Thus, this information can be used to reduce risk for patients

Quiz

- What are the characteristics of a drug that increase the need for dosage adjustment when renal function drops?
 - A. Highly metabolized
 - B. Highly water soluble
 - C. Narrow therapeutic range
 - D. Metabolized to an inactive compound
 - E. B and C
 - F. A and C

Is There a Need?

Papaioannou A, et al. Assessment of adherence to renal dosing guidelines in LTC facilities. *J Am Ger Soc.* 2000;48:1470-3.

- 34.1% of Rx were considered inappropriate for calculated CrCl
- 42.3% of residents given a drug under review (18 drugs were considered) had at least 1 inappropriate prescribed dose
- Age, weight, number of prescriptions, and number of physicians prescribing at site were predictive of receiving an inappropriate dose

Is There a Need?

Long CL, et al. Compliance with dosing guidelines in patients with chronic kidney disease. *Ann Pharmacother* 2004;38:853-8.

- Evaluated 6 articles from inpatient, long term care (LTC), and ambulatory settings
- Renal dosing noncompliance ranged from 19 to 67% in hospitals.
- Noncompliance in LTC facilities was 34% (article described in previous image)
- Though published studies not available for ambulatory settings, an abstract indicated 69% noncompliance

Is There a Need?

Yap C, et al. Medication dosing errors for patients with renal insufficiency in ambulatory care. Joint Commission J Qual Patient Safety. 2005;31:514-21.

- 224 patients with CrCl <50 ml/min identified over a year period in clinic
- 127 of these had no documentation in chart of renal insufficiency
- 157 (70%) received 1 or more drugs that are highly renally eliminated
- 207 drugs required adjustment with 52 (25%) inappropriately high doses

Is There a Need?

Van Dijk EA, et al. Drug dosage adjustments according to renal function at hospital discharge. Ann Pharmacother 2006;40:1254-60.

- Researchers determined need at discharge for dosage adjustment for patients with CrCl < 51ml/min/1.73m²
- During study period 36.6% of discharged patients had CrCl < 51 with dosage adjustment needed in 411 of 1718 Rx (24%)
- Adjustment had only occurred in 58.9%, thus patients are being missed
- Authors recommended an alerting system

Is There a Need?

Rahimi AR, et al. Improper renal dosing in long-term-care facilities. *S Med J* 2008;101:802-5.

- Data collected at two facilities
- 53 medications evaluated
- Of 90 patients, 56 (62%) had medications that required adjustment; 26 (46%) did not have the adjustment made
- Authors believed that age and renal function were often not considered

Is There a Need?

Markota NP, et al. Inappropriate drug dosage adjustments in patients with renal impairment. *J Nephrol* 2009;22:497-501.

- Used MDRD; Patients < 60 ml/min
- 22.6% of patients at discharge < 60 ml/min
- Dosage adjustment was necessary for 19.6% of prescribed drugs but was only done in 47.4% of the cases
- Digoxin, metformin, and ACE inhibitors with spironolactone most frequently culprits
- Authors concluded that drug dosing could be improved and *family physicians* could play role

Quiz

- Based on the previously reviewed studies, it appears that about 30% to 50% of patients with diminished renal function are not having their doses adjusted appropriately (according to the study authors)
 - A. True
 - B. False

Is There a Need?

- Studies focus on general guidelines
- Little to no documentation of adverse events in patients without adjustments
- No cost estimates of providing services
- While I believe that it is important to adjust doses in reduced renal function, there should be evaluations of adverse impacts when they aren't adjusted to help increase the value of the service

Renal Dosing Approaches

Dettli method

- Can adjust dose, interval, or both using the approach developed by Dettli
- Dosage adjustment factor = Q
- $Q = 1 - [f_e (1 - \frac{CrCl}{CrCl_{normal}})]$
- f_e = fraction excreted unchanged in the urine

Renal Dosing Approaches

Dettli method

- $Q = 1 - [f_e (1 - \frac{CrCl}{CrCl_{normal}})]$
- $Dose_R = Q \cdot Dose_{Normal}$
- $Interval_R = Interval_{Normal} \div Q$
- $Dose_R = Q \cdot (D_N \div T_N) \cdot T_R$

Renal Dosing Approaches

Detli method – Example drug given 300 mg every 8 hours, $f_e = 0.8$, CrCl 60 ml/min

- $Q = 1 - \left[f_e \left(1 - \frac{CrCl_{patient}}{CrCl_{normal}} \right) \right]$
- $Q = 1 - [0.8 (1 - 60/120)] = 0.6$
- $Dose_R = 0.6 \cdot 300 \text{ mg} = 180 \text{ mg}$
- $Interval_R = 8 \text{ hr} \div 0.6 = 13.3 \text{ hr}$
- $Dose_R = 0.6 \cdot (300\text{mg} \div 8) \cdot 12$
- $Dose_R = 270 \text{ mg every } 12 \text{ hr}$

Renal Dosing Approaches

Package Inserts

- Give 50% of dose in patients with CrCl \leq 50 ml/min
- Reduce doses
- Increase interval
- Complex scales of dose and interval
- All are limited by available dose forms and logical dosing intervals

Renal Dosing Approaches

Tobramycin Example

Dosing interval in renal impairment:

Conventional dosing:

- CrCl \geq 60 ml/min: Administer every 8 hrs
- CrCl 40-60 ml/min: Administer every 12 hrs
- CrCl 20-40 ml/min: Administer every 24 hrs
- CrCl 10-20 ml/min: Administer every 48 hrs
- CrCl <10 ml/min: Administer every 72 hrs

Renal Dosing Approaches

Aminoglycoside Large Dose – 24 hour Interval Example

Table 4-8. Once-Daily Dosing Approaches, Dose Based on CrCl

CrCl, ml/min	Example A	Example B
	<u>Dose mg/kg</u>	<u>mg/kg</u>
\geq 80	5.1	4.0
61–80	3.9	3.25
51–60	3.6	3.25
30–50	3.0	2.5
<30	Not used	2.0

a Doses are based on ABW unless ABW/IBW ratio is \geq 1.35, then an adjusted body weight (BW_{adj}) is used (see Step 3b in the dosing strategies section on determining dosing weight and volume of distribution for determination of BW_{adj}).

b Doses based on ABW.

Renal Dosing and Pharmacy

- Since the early days of therapeutic monitoring and pharmacokinetics, pharmacists have adjusted doses of medications using drug concentrations or measures of organ function
- The breadth of coverage is wide today but the depth is uncertain

Renal Dosing and Pharmacy

Gupta SR, et al. Monitoring of pharmacy staffing, workload, and productivity in community hospitals. *Am J Health-Syst Pharm.* 2006;63:1728-34.

- Of 110 community hospitals, 93 (84.5%) indicated they provided a *renal dosing program*
- 88.2% provided *PK dosing and monitoring services*
- 81.8% provided *drug therapy monitoring*
- The productivity systems of the hospitals didn't account for clinical services well

Renal Dosing Through the Years

Berbatis CG, et al. 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.

- Pharmacists checked for elevated serum creatinine in patients
- Evaluated medications patients were receiving for renally excreted drugs
- Provided advice to the medical officers when regimens were in excess of recommendations or when contraindicated medications prescribed

Renal Dosing Through the Years

Libiszewski D. The development of a drug dosage adjustment service for patients with renal impairment. J Clin Hosp Pharm. 1981;6:39-49.

- The service was made available for nephrotoxic drug dosing using nomograms to alter therapy
- About 80% of requests were for dosage adjustment of gentamicin in renal failure
- Author believed this service can be offered without difficulty by hospital pharmacists

Years

Peterson JP, et al. Using serum creatinine concentrations to screen for inappropriate dosage of renally eliminated drugs. Am J Hosp Pharm 1991;48:1962-4.

- Clinical pharmacist reviews lab data for patients with Scr > 1.5 mg/dl
- Next, calculates CrCl and screens patient charts for drugs renally eliminated
- Over 13 months, 2341 patients screened, 162 recommendations made, and 142 (88%) accepted
- Antimicrobials and H₂ blockers primary
- Took 20 to 30 minutes of pharmacist time/day

Renal Dosing Through the Years

Golightly LK, et al. Pharmacist monitoring of drug therapy in patients with abnormal serum creatinine levels. Hosp Pharm 1993;28:725-7.

- Pharmacist responsible for monitoring elevated Scr and for determining if renally eliminated drugs were used appropriately
- Over 2 years, 627 patients were monitored and 233 had changes in therapy based on the pharmacist's recommendations
- Antimicrobials involved in 55% of changes
- An assessment of the efficacy revealed no evidence of therapeutic failure or toxicity based on the recommendations

Renal Dosing Through the Years

McMullin ST, et al. Automated system for identifying potential dosage problems at a large university hospital. *Am J Health-Syst Pharm.* 1997;54:545-9.

- Pharmacy department developed software to screen drug therapy for potential problems with 35 targeted drugs
- One aspect was calculating CrCl and then verifying that dosages are correct for renal drugs
- Over 6 months the system detected 2859 (10% of total) potential dosage problems
- The program recommended dose decrease in 70% and increase in 30%
- Physicians contacted for 41% (1163) of the cases and they altered doses as recommended in 75%

Renal Dosing Through the Years

Nash I, et al. Reducing excessive medication administration in hospitalized adults with renal dysfunction. *Am J Med Qual* 2005;20:64-9.

- Automated system added to CPOE program to detect excessive dosing in renal patients
- Baseline rate of excess dosing was 23.2% (doses needed to be adjusted)
- Rate fell to 17.3% with nurse feedback and 16.8% with pharmacist feedback
- Conclusion: Automated detection and routine feedback reduces the rate of excessive doses in hospitalized patients with renal insufficiency

Quiz

- Based on the data presented, it can be seen that pharmacists' recommendations to prescribers to adjust doses of renally excreted drugs in patients with reduced renal function are frequently accepted and that the outcomes of the patients are improved.
A. True
B. False

Alternative Approaches

Oppenheim MI, et al. Impact of a computerized alert during physician order entry on medication dosing in patients with renal impairment. Proc AMIA Symp. 2002:577-80.

- Alerting by the system led both new and experienced physicians to alter doses
- Changes were made an average of 52% of the time but as high as 71% in certain groups

Issues

- Creatinine standardization
- Which equation should be used to predict CrCl for dosing decisions or CKD staging
- Do the equations fit individual patients
- Will CPOE take over

Issues

- Can pharmacists do it better than others
- Downstream implications of changes (e.g., too low a dose)
- Doses can be decreased or increased – don't forget that someone might have put on too low
- Virtually no studies on value of dosing changes or danger of not changing

GFR and Creatinine

Freedberg DE. To eGFR or not to eGFR. *Kidney International* 2009;76:129-30.

- GFR is not immutable – it can change based on time of day, salt intake, volume status, blood pressure, diet, illness, and obesity
- Creatinine is somewhat hard to measure – the concentration is low and the assay to measure is troublesome and varies between labs.
- Labs to begin calibrating to “gold standard”

Estimating Methods

Freedberg DE. To eGFR or not to eGFR. *Kidney International* 2009;76:129-30.

- MDRD and Cockcroft-Gault developed in certain types of patients
- Both have been validated in other patient groups (e.g., obese, diabetics, cancer, Japanese, South Asians, Chinese, Swedes, older patients) with subsequent “modifications”
- “Which equation would I use for an elderly diabetic, Latino-Chinese patient?”

Estimating Methods

- Many estimating methods exist though our research indicates that Cockcroft-Gault remains most widely used by pharmacists in the USA
- The following demonstrate CG and other equations that can be used

Markers of Renal Function

Renal plasma/blood flow	<i>p</i> -Aminohippurate (PAH) ¹³¹ I-Orthoiodohippurate (¹³¹ I-OIH) ^{99m} Tc-mercaptoacetyltriglycine (^{99m} Tc-MAG3)
Glomerular filtration rate	Inulin, sinistrin Iothalamate Iohexol ^{99m} Tc-diethylenetriaminepentaacetic acid (^{99m} Tc-DTPA) ¹²⁵ I- Iothalamate Creatinine Cystatin C Beta Trace Protein
Tubular function	Albumin -- Micro albuminuria β_2 -Microglobulin Retinol-binding protein (RBP) Protein HC (α_1 -microglobulin) <i>N</i> -Acetylglucosaminidase (NAG) Alanine aminopeptidase (AAP) Adenosine binding protein (ABP)

Factors That May Alter Creatinine Clearance Determinations

Analytical	Physiologic
Acetoacetate	Age, weight, gender
Ascorbic acid	Diet
Cephalosporins (cephalothin, cefazolin, cephalixin, cefoxitin, cefaclor, cephradine)	Diurnal variation Cimetidine
Dobutamine	Trimethoprim
Dopamine	Probenecid
5-Flucytosine	Exercise
Fructose	
Glucose	
Protein	
Pyruvate	
Uric acid	

Equations for the Estimation of Creatinine Clearance

in Adults with Stable Renal Function

Cockcroft and Gault	Men: $CL_{cr} = (140 - \text{age}) \text{ ABW} / (S_{cr} \times 72)$ Women: $CL_{cr} \times 0.85$
Jelliffe I	Men: $CL_{cr} = (100/S_{cr}) - 12$ Women: $CL_{cr} = (80/S_{cr}) - 7$
Jelliffe II	Men: $CL_{cr} = 98 - [0.8 (\text{age} - 20)]/S_{cr}$ Women: $CL_{cr} \times 0.9$
Mawer et al.	Men: $\text{IBW} [29.3 - (0.203 \times \text{age})] [1 - (0.03 \times S_{cr}) / (14.4 \times S_{cr})]$ Women: $\text{IBW} [25.3 - (0.175 \times \text{age})] [1 - (0.03 \times S_{cr}) / (14.4 \times S_{cr})]$
Hull et al.	Men: $CL_{cr} = [(145 - \text{age})/S_{cr}] - 3$ Women: $CL_{cr} \times 0.85$

Equations for the Estimation of Creatinine Clearance in Obese Adults with Stable Renal Function	
Cockroft and Gault	Men: $CL_{cr} = (140 - \text{age}) \frac{\mathbf{ABW}}{(S_{cr} \times 72)}$ Women: $CL_{cr} \times 0.85$
Cockroft and Gault	Men: $CL_{cr} = (140 - \text{age}) \frac{\mathbf{IBW}}{(S_{cr} \times 72)}$ Women: $CL_{cr} \times 0.85$
Cockroft and Gault	Men: $CL_{cr} = (140 - \text{age}) \frac{\mathbf{AdjBW}}{(S_{cr} \times 72)}$ Women: $CL_{cr} \times 0.85$
Salazar & Corcoran	Men: $CL_{cr} \text{ (mL/min)} = [(137 - \text{Age}) \times [(0.285 \times \text{IBW}) + (12.1 \times \text{Ht}^2)]] / (51 \times \text{Scr})$
	Women: $CL_{cr} \text{ (mL/min)} = [(146 - \text{Age}) \times [(0.287 \times \text{IBW}) + (9.74 \times \text{Ht}^2)]] / (60 \times \text{Scr})$

When using CG, which body weight do you use?

- Actual body weight
- Ideal body weight
- Adjusted body weight
- A combination of the above,
depending on level of obesity

Equations for the Estimation of *Glomerular Filtration Rate* in Adults with Stable Renal Function

Levey et al. GFR = $170 \times (S_{cr})^{-0.999} \times [age]^{-0.176} \times [0.762 \text{ if patient (MDRD6) is female}] \times [1.180 \text{ if patient is black}] \times [SUN]^{-0.170} \times [Alb]^{0.318}$

Levey et al. GFR = $186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if patient (MDRD4) is female}) \times (1.210 \text{ if patient is black})$
Non IDMS

Levey et al. GFR/1.73 m² = **175** $\times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ (MDRD4) if patient is female}) \times (1.210 \text{ if patient is black})$
IDMS

Table 2. The CKD-EPI Equation for Estimating GFR on the Natural Scale*

Race and Sex	Serum Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	Equation
Black		
Female	≤ 62 (≤ 0.7)	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	> 62 (> 0.7)	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤ 80 (≤ 0.9)	$GFR = 163 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	> 80 (> 0.9)	$GFR = 163 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤ 62 (≤ 0.7)	$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
	> 62 (> 0.7)	$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤ 80 (≤ 0.9)	$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$
	> 80 (> 0.9)	$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$

Levey, A. S. et. al. Ann Intern Med 2009;150:604-612

Equations for the Estimation of Glomerular Filtration Rate based on Cystatin C in Adults with Stable Renal Function	
Hoek's 2003	$GFR = -4.32 + (80.35 / S_{\text{cystatin C}})$
Grubb's 2005	$GFR = 86.49 \times (S_{\text{cystatin C}})^{-1.686} \times (0.948 \text{ if patient is female})$
Grubb's 2 2005	$GFR = 99.19 \times (S_{\text{cystatin C}})^{-1.713} \times (0.823 \text{ if patient is female})$
Larsson's 2004	$GFR = 77.24 \times (S_{\text{cystatin C}})^{-1.2623}$
Sjostrom's 2005	$GFR = [124 / S_{\text{cystatin C}}] - 22.3$

Concerns with MDRD

- Clinical labs using IDMS vs. standard Pcr assay
- Labs report "eGFR" values ONLY when GFR < 60 ml/min/1.73m² (otherwise reported as "GFR > 60 ml/min/1.73m²")
- Clinicians concerned about unit conversion (to ml/min) and patients with GFR 60-80 ml/min/1.73m²
- FDA label gives renal drug dosing recommendations based on CrCl (Cockcroft-Gault) not MDRD
- Studies evaluating relationship between MDRD (eGFR) and total drug clearance currently not available

Cockcroft-Gault vs MDRD

Gill J, et al. Use of GFR equations to adjust doses in an elderly, multi-ethnic group – a cautionary tale. *Nephrol Dial Transplant* 2007;22:2894-99.

- MDRD (re-expressed for isotope dilution mass spectrometry-based creatinine) vs CG corrected for BSA
- 180 pts; mean 85 YO; 30% Asian
- Mean MDRD – 73 ml/min/1.73²
- Mean CG – 52 ml/min/1.73m²
- Discordant estimations (reclassification of 1 stage of CKD) in > 60%
- “...interchangeable use cannot be advocated in the dosing of medications...” until validated

Cockcroft-Gault vs MDRD

Golik MV, Lawrence KR. Comparison of dosing recommendations for antimicrobial drugs... *Pharmacotherapy* 2008;28:1125-32.

- 207 adults with decreased renal function but not on dialysis
- Estimated “GFR” by two MDRD and four CG approaches
- Determined doses for 4 antimicrobials based on MDRD unadjusted for BSA and CG based on ideal body weight
- Discordance in dose occurred in 23-36% of doses and was always higher with MDRD

Cockcroft-Gault vs MDRD

Hermesen ED, et al. Comparison of MDRD and CG equations for dosing antimicrobials. *Pharmacotherapy* 2009;649-55.

- 372 pts with CKD or AKD
- 99.1% of cases with discordant dose recommendations would receive higher dose with MDRD estimations
- GFR was significantly higher with MDRD in both AKD and CKD, but highest with CKD
- An expert also rated GFR higher than CG but similar to MDRD
- Specific dose changes were different in ~40%

Cockcroft-Gault vs MDRD

Moranville MP, et al. Implications of using MDRD vs CG equations for renal dosing adjustments. *Am J Health-Syst Pharm* 2009;66:154-61.

- 4698 pts with stage III – V CKD analyzed
- Dosing simulations using both methods were compared to manufacturer recommendations
- MDRD overestimated need for adjustments for CrCl < 30 ml/min/1.73m² and under-estimated for CrCl > 50 ml/min/1.73m²
- Total dosing errors with MDRD were 9.8% to 18.2%
- Significant differences existed between CG and MDRD for spot dosing adjustments

Quiz

- Based on the presentation it can be said that:
 - A. MDRD leads to more frequent dosage adjustment than Cockcroft-Gault (CG)
 - B. MDRD is overall a better method of estimating renal function for dosing
 - C. MDRD may be the better approach for staging chronic renal dysfunction compared to CG
 - D. All of the above

Conclusions

- Pharmacists have been providing renal dosage adjustments for many years
- The implications of adjusting doses of medications by such services, CPOE dosing recommendations, or guidelines is rarely evaluated in terms of patient outcomes in a controlled fashion
- There are many inconsistencies in approaches taken to estimate CrCl or GFR in studies for various patient population

Conclusions

- Dosing guidelines by manufacturers are generally based on creatinine clearance (rather than GFR) and estimate of renal function by the “Cockcroft-Gault” equation when a method is suggested
- Standardization of reporting methods is essential
- Estimates or measurement of CrCl should likely be used until MDRD verified