US Renal Network

Defining Normal Kidney Function in Phase I Clinical Trials: An Emerging Issue

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INTRODUCTION

Though it is generally accepted that renal function declines with age, equations that estimate glomerular filtration rate (GFR) or creatinine clearance (CrCl) do not have defined age-adjusted normal ranges. Additionally, the Modified Diet in Renal Disease Study (MDRD) equation and the Cockcroft-Gault creatinine clearance (CG) equation have been reported to provide discrepant results within patients with normal renal function. This could lead to misclassification of kidney function when attempting to identify normal renal function, age-matched controls for phase I/II pharmacokinetic trials involving investigational pharmaceutical compounds. The U.S. Renal Network is the largest phase I pharmacokinetic research group of renally impaired patients in the US. Collectively, it provides a unique setting to study the effect of age on the performance of the MDRD and the CG equation when evaluating patients with normal renal function.

METHODOLOGY

- We reviewed pharmacokinetic trial data from 2003 to 2009 generated by 3 phase I clinical research sites [Orlando Center for Clinical Research (OCCR), New Orleans Center for Clinical Research (NOOCR), and DaVita Clinical Research (DCR)] within the US Renal Network, to identify research participants with normal renal function.
- Normal renal function was defined as a creatinine value of ≤1.2.
- Simultaneous results for Cockcroft-Gault (CG), the Modified Diet in Renal Disease Study (MDRD) equation and 24-hour creatinine clearance (CrCl) were compared.

RESULTS

- 450 subjects with both an MDRD and a CG result were identified.
- Only 95 subjects had a concomitant 24-hour Creatinine Clearance.

Table1. MDRD, CG and CrCl by Age Categories

		MDRD		CG		CrCl	
Age Strata	Sex	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
<40	F	20	76.1 ± 12.0	20	99.3 ± 22.6	2	68.5 ± 6.4
	M	33	92.7 ± 12.5	29	126.9 ± 23.4	3	100.3 ± 11.9
	All	53	86.4 ± 14.7	49	115.6 ± 26.7	5	87.6 ± 19.6
40-49	F	38	74.9 ± 9.4	36	96.5 ± 17.6	8	83.5 ± 18.1
	M	18	90.5 ± 17.6	17	130.2 ± 31.6	2	132.5 ± 24.8
	All	56	79.9 ± 14.5	53	107.3 ± 27.7	10	93.3 ± 27.4
50-59	F	118	74.4 ± 11.0	113	88.3 ± 16.6	35	93.7 ± 16.6
	M	64	80.9 ± 13.6	60	102.3 ± 22.0	11	125.8 ± 33.5
	All	182	76.7 ± 12.3	173	93.1 ± 19.8	46	101.4 ± 25.5
60-69	F	78	77.0 ± 16.4	70	89.8 ± 21.3	23	89.8 ± 17.7
	M	38	84.2 ± 14.8	34	99.2 ± 18.8	5	132.8 ± 28.7
	All	116	79.4 ± 16.2	104	92.9 ± 20.9	28	97.5 ± 25.7
70-79	F	30	68.1 ± 14.6	30	67.8 ± 15.9	9	61.3± 19.2
	M	23	81.5 ± 11.4	22	84.8 ± 13.5	1	96.0
	All	53	73.9 ± 14.8	52	75.0 ± 17.0	10	64.8 ± 21.1
All (MDRD/CG)		460	78.5 ± 14.5	431	95.2 ± 24.2		
All with CrCl		99	73.4 ± 10.4	99	89.5 ± 19.7	99	95.1 ± 26.9

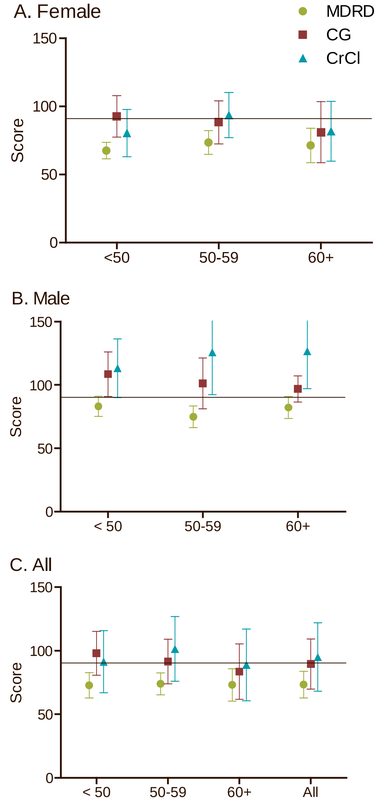

Figure 1. MDRD, CG, and CrCl for patients with CrCl score

SUMMARY of RESULTS

- The eGFR mean of trial participants (as measured by MDRD) was less than 80 ml/min among all men and women aged 40 to 79.
- If normal renal function is defined as a GFR >90 ml/min, few, if any, age-matched subjects would qualify as normal using the MDRD eGFR. No women, in any age category, had a mean MDRD of >90 ml/min (Table 1).
- CG estimates, as expected, proved to be higher on average than MDRD, with the most marked difference at younger ages (Figure 1).
- 24-hour creatinine clearances (n=99) were 21.7 ml/min higher than the mean MDRD estimate and 5.6 ml/min higher that the mean CG estimate (Table 1, Figure 1C).

KEY LEARNINGS

- ✓ A proposed revision of current FDA guidance on conducting pharmacokinetic drug studies in renal impairment subjects defines normal kidney function >90 ml/min but does not specify a method of estimation.
- ✓ A distinction should be made between the methods of estimation used.
  - Estimation using CG is predictable for patients with normal function, but not for patients with renal impairment.
  - Estimation using MDRD is predictable for patients with renal impairment patients, but not for patients without renal disease.
- ✓ A lower, or age-adjusted normal eGFR is warranted for phase I studies.

We express our sincere appreciation to the US Renal Network, NOCCR, OCCR and DCR staff who are committed to research and quality data. We thank DaVita Clinical Research® for support in preparing this poster. DCR is committed to advancing the knowledge and practice of kidney care.

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American Society of Nephrology RenalWeek 2010, Denver, CO