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RESEARCH LETTER

Concordance Between Iothalamate and Iohexol Plasma Clearance

To the Editor:

Iohexol is regarded as an accurate filtration marker for measuring GFR. Recently, Soveri et al[1] concluded that plasma clearance of iohexol could be considered a valid alternative to the gold standard, urinary clearance of inulin. Because inulin urinary clearance is cumbersome and costly, iohexol and iothalamate clearance have become popular in Europe and the United States, respectively. To advance GFR research, it therefore seems relevant to directly compare these 2 methods. Seegmiller et al[2] recently highlighted discordance between urinary clearance of iothalamate and iohexol measured by LC-MS/MS; iohexol clearance was ∼15% lower than iothalamate clearance. However, at least for iohexol, plasma disappearance is generally used in clinical practice and research.[3-5]

Here, we concomitantly measured GFR by plasma clearance of both iohexol and iothalamate in 102 patients. Indications for GFR measurement were kidney function evaluation in either potential living kidney donors or patients whose serum creatinine–based GFR estimation was suspected as inaccurate.[6] The protocol had ethics committee approval (Belgian number: B7072014220701). All patients signed informed consent. Five mL of iohexol (Omnipaque 240, 240 mg/mL; GE Healthcare BVBA) and 5 mL of iothalamate (Conray 30; iothalamate meglumine, 141 mg/mL; Covidien) were administered simultaneously in the same vein (antecubital, forearm, or hand vein) and flushed with 10 mL of normal saline solution. Blood samples were obtained using the contralateral arm at 120, 180, 240, and 300 minutes after injection and GFR was calculated as per Brochner-Mortensen.[7] Samples were centrifuged for 10 min at 3,000 g within 2 hours of collection and stored at −80°C. Iohexol was measured by 2 methods (HPLC, as previously described,[8] and LC-MS/MS); iothalamate was measured by LC-MS/MS (analytical methods in Item S1). Our laboratory participates in interlaboratory quality control performed by Equalis AB (Uppsala, Sweden) using both methods 4 times a year. Clearance results were analyzed by Passing-Bablok regressions and concordance correlation coefficient (CCC). For Bland-Altman analysis, we calculated relative bias as the mean difference between iohexol and iothalamate divided by the mean of iohexol and iothalamate results. Accuracy within 30% and 15% were computed as percentage of iothalamate results ±30% or ±15%, respectively, of the mean of iohexol and iothalamate results.

Clinical characteristics of the study population are given in table *a* of Item S1. Mean GFRs measured by iohexol using HPLC and LC-MS/MS were 77 ± 25 and 71 ± 25 mL/min/1.73 m^2, respectively, and by iothalamate, 80 ± 29 mL/min/1.73 m^2. Figure 1 shows Passing-Bablok regression comparisons; CCC analyses are in figures *a* and *b* of Item S1. Relative bias between iohexol and iothalamate (HPLC and LC-MS/MS) results were −2% ± 13% ($P = 0.2$) and −11% ± 9% ($P < 0.001$), respectively (Fig 2). Accuracy within 30% was 98% and 99% ($P = 0.9$), and within 15% was 80% and 74% ($P = 0.4$). Item S1 figures *c* to *e* show agreement analyses between GFR measured by iohexol using HPLC or LC-MS/MS.

We found acceptable concordance between iohexol and iothalamate plasma clearance compared to the intraindividual variation of measured GFR of ∼10%.[9] Using HPLC to measure iohexol, we detected no significant difference between iohexol and iothalamate clearance, but as in the study by Seegmiller et al,[2] using LC-MS/MS–measured iohexol gave significantly lower iohexol versus iothalamate clearance. Thus, the method for measuring iohexol or iothalamate can influence results. Additional studies are necessary to explain the analytical bias observed in the 2 methods. In the absence of urinary inulin clearance, we cannot definitively conclude which method is best. However, because iothalamate is secreted by tubules, the 10% lower results observed with LC-MS/MS iohexol plasma clearance might be closer to the true GFR value.

Plasma clearance slightly overestimates urinary clearance, whatever the marker used.[10] However, we think that plasma clearance is the best compromise between physiology and feasibility in clinical routine. Plasma clearance is far less cumbersome (and costly), especially in elderly and young children, for whom urine collection is very challenging. As demonstrated here, the easy-to-use plasma method gives comparable results using either iohexol or iothalamate. The concordance is sufficient to recommend either of these 2 methods in daily practice. Still, depending on the method used to measure iohexol, a slight bias may be observed, which should be taken into consideration in clinical research settings.

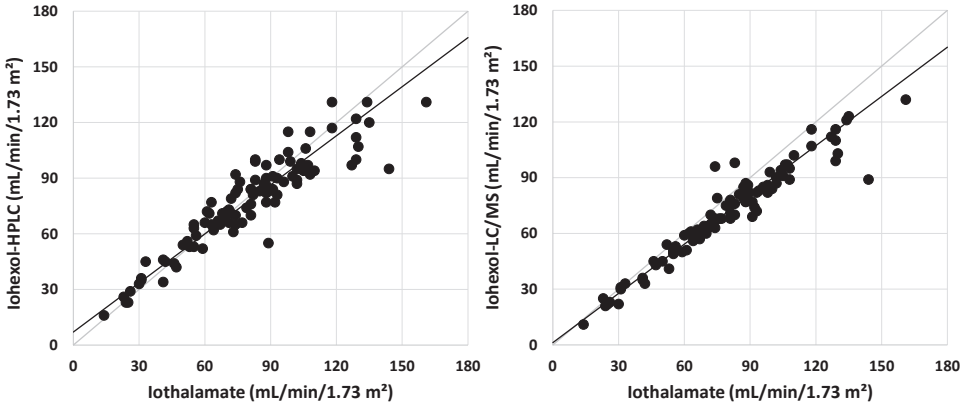

Figure 1. Passing-Bablok regressions: comparison of GFR measured by iohexol (y-axis) and iothalamate (x-axis). With iohexol measured by HPLC (high-performance liquid chromatography; left panel), the equation for the regression line (black line; with 95% confidence intervals) is y = 0.88x + 7 (0.82, 0.94; 3, 11). With iohexol measured by LC-MS/MS (liquid chromatography–tandem mass spectrometry; right panel), the equation for the regression line (black line; with 95% confidence intervals) is y = 0.88x + 1 (0.85, 0.92; −1, 4). The grey line is the identity line.

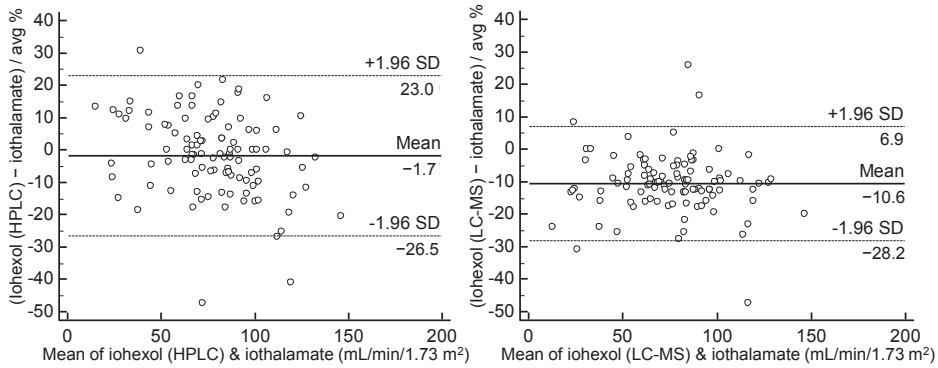

Figure 2. Bland-Altman analysis: comparison of GFR measured by iohexol and iothalamate (iohexol measured by HPLC [left], iohexol measured by LC-MS/MS [right]).

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Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, and the Editor-in-Chief.

Supplementary Material

Item S1. Detailed methods, clinical characteristics, and CCC and agreement analyses.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.01.007) is available at www.ajkd.org

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