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RESEARCH

Improved correction formulas to estimate iohexol clearance from simple models

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To the editor,

Measuring glomerular filtration rate by iohexol plasma clearance has become a preferred method in clinical practice and research [1–9], but ambiguities remain regarding the choice of pharmacokinetic modeling when evaluating iohexol concentration. We recently showed that a three-compartment pharmacokinetic model provides better iohexol clearance estimates than the two-compartment approach in elderly subjects in the Berlin Initiative Study (BIS) [7, 8]. However, implementation of the presented model in clinical and research practice is complicated by the required technical expertise and the complexity of Bayesian software [7]. A viable alternative could be the use of correction formulas which rely on traditional one- or two-compartment models and correct the obtained clearance estimates for the bias introduced by the omission of compartments [9–14]. Well-known examples for established correction formulas are the Bröchner-Mortensen (BM) equation [12] and the further simplified Chantler (Ch) formula [14] based on a one-compartment model, which have recently been shown to perform well in iohexol data from the BIS [9]. Such an evaluation remains to be carried out based on a three-compartment model, which is the subject of this letter.

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Data from the BIS, including 546 individuals with data obtained up to 300 min post-injection, were evaluated [7, 8]. One-, two-, and three-compartment models were used to estimate iohexol clearance (CL1, CL2, and CL3), respectively. CL1 was estimated based on the slow component of iohexol concentrations 120 to 300 min post-dose, CL2 was estimated based on the protocol by Schwartz et al. [11] as carried out in the BIS [8], and CL3 was estimated using the empirical Bayes approach based on the three-compartment model [7]. Equations resembling the BM and Ch formulas were then fitted to correct CL1 and CL2 results, using CL3 as the reference (Table 1) [12, 14]. A leave-one-out cross-validation [15] was utilized to assess the bias and root mean squared error (RMSE), as well as to evaluate Lin's concordance correlation coefficient (CCC) [16] and the relative total deviation index (TDI) for a range of coverage probabilities (CP) [17]. A TDI $\leq$ 10% for a CP of 90% (TDI_{90}) and an at least substantial CCC of $\geq$ 0.95 were considered optimal. R 4.2.1 [18] and NONMEM 7.4.2 [19] were used as statistical software.

BM- and Ch-like equations performed similarly well (Table 1), with an absolute bias < 1 mL/min, an RMSE between 2.92 and 4.08 mL/min, and a substantial concordance for all equations. The TDI_{90} goal was achieved with Eqs. 3 and 4 based on two compartments, while it was missed with Eqs. 1 and 2 based on one compartment. Differences between BM-like and Ch-like equations were negligible with equations based on two compartments, while the BM-like equation provided a notably lower absolute bias than the Ch-like equation in the case of one compartment (− 0.0949 versus − 0.357 mL/min). In summary, our evaluation demonstrates that correction formulas in conjunction with one- or two-compartment models can provide adequate clearance estimates with only a minimal loss in accuracy and precision compared to a three-compartment model. When one-compartment estimates are available, the BM-like correction formula might be a good choice, while the simple

Table 1 Performance of correction formulas based on leave-one-out cross-validation, comparing iohexol clearance estimates obtained from different correction formulas to reference clearance values from three-compartment model

Nr.	Equation	Bias (mL/min) mean (95% CI)	Relative bias (%) mean (95% CI)	RMSE (mL/min)	CCC	TDI_{90} (%)
1 (BM)	$CL=0.872\times CL1-0.000560\times CL1^2$	−0.0949 (−0.428 to 0.238)	−0.103 (−0.616 to 0.411)	3.97	0.974	10.6
2 (Ch)	$CL=0.824\times CL1$	−0.357 (−0.698 to −0.016)	−0.953 (−1.50 to −0.409)	4.08	0.974	11.5
3 (BM)	$CL=0.894\times CL2+0.0000246\times CL2^2$	−0.0415 (−0.288 to 0.205)	−0.0331 (−0.411 to 0.344)	2.94	0.986	7.71
4 (Ch)	$CL=0.896\times CL2$	−0.0313 (−0.277 to 0.214)	−0.0022 (−0.378 to 0.374)	2.92	0.986	7.68

CL iohexol clearance estimates obtained from different correction formulas, *CL1* one-compartment clearance estimates, *CL2* two-compartment clearance estimates, *BM* Bröchner-Mortensen–like equation, *Ch* Chantler–like equation, *CI* confidence interval, *RMSE* root mean square error, *CCC* Lin's concordance correlation coefficient, TDI_{90} total deviation index for a coverage probability of 90%

Ch-like formula might be sufficient if two-compartment estimates are available. This provides the means to efficiently estimate iohexol clearance in settings where complexities and costs associated with the implementation of a Bayesian model are prohibitive. Whether the slight loss of accuracy and precision compared to the three-compartment model is acceptable depends on the clinical context and should therefore be judged on a case-by-case basis. Further validation in diverse patient populations is required, and the evaluation of additional, potentially non-linear correction formulas might provide further improvements.

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Declarations

Competing interests The authors declare no competing interests.

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