BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12602

Cystatin C as a potential biomarker for dosing of renally excreted drugs

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Keywords
cystatin C, renal function, renal elimination, pharmacokinetics, clearance, glomerular filtration rate, dose regimen

Received
4 August 2014

Accepted
30 January 2015

Accepted Article Published Online
5 February 2015

The objective of the present study was to review the available pharmacokinetic evidence for the utility of cystatin C (CysC) as a marker of renal function to predict the dose of renally excreted drugs.The bibliographic search used PubMed and EMBASE databases, from its inception through to January 2014, with the following keywords 'pharmacokinetics' and 'cystatin C'.Sixteen pharmacokinetic publications were identified and seven drugs primarily excreted by the kidney were studied. Among them, only one study was performed in children, the others were performed in adults and/or elderly subjects, either healthy volunteers or patients with variable clinical conditions, such as cystic fibrosis and cancer. Most of studies (n = 13/16) demonstrated that CysC was better correlated with clearance/trough concentration of evaluated drugs compared with creatinine.Our review supports that CysC is a good marker of renal function to predict dose of renally excreted drugs. Efforts should be made to evaluate the impact of CysC in special populations in order to define its clinical value in dosing optimization.

Introduction

Renal function has a major impact on the pharmacokinetics and dose of predominantly renally excreted drugs. Quantification of renal function is central for dosage adjustment in patients with impaired renal function (i.e. in critically ill patients, the elderly) or in patients with renal immaturity (i.e. neonates particularly if premature), as renal function fluctuates considerably in such conditions [1, 2].

Renal elimination is a drug-dependent process. Glomerular filtration rate (GFR) is, in general, accepted as the best overall measure of renal function and used for dosage adjustment. In clinical practice, the most common method to determine GFR is based on serum creatinine concentrations, allowing the calculation of creatinine clearance. However, the use of creatinine as a marker of GFR has its own limitation. Creatinine is not only filtered, but also secreted by the renal proximal tubules. The calculated creatinine clearance value may overestimate the true GFR, in particular for patients with decreased renal function [3–6] and be inaccurate in neonates [7, 8]. Additional methods, which used exogenous compounds (iohexol, inulin, sinistrin, radiolabelled isotope, aminoglycosides) [9–11], exist to estimate/predict GFR, but mainly for research purposes, as they are labour intensive, time consuming, expensive to perform and require a strict procedure of administration, making them difficult to use in routine clinical practice [12–16].

An alternative biomarker of GFR would be of great interest and many studies have been conducted in recent years to evaluate cystatin C (CysC) [17–21]. CysC is a non-glycosylated basic protein with a low molecular weight of 13 kDa. It is produced at a constant rate by all nucleated cells [22] and not bound to plasma proteins. CysC is freely filtered through the renal glomerulus and subsequently reabsorbed and catabolized in proximal renal tubules [23–25]. The results from previous studies have shown that serum CysC was an adequate marker of GFR and significantly outperformed serum creatinine for the detection of impaired GFR in critically ill patients [26]. Meta-analyses also indicated that CysC was superior to serum creatinine in the determination of GFR injury [27–29].

Despite these results, the use of CysC for drug dosage adjustment remains limited. The purpose of the present study was to review the available pharmacokinetic evidence for the utility of CysC as a marker of renal function to predict dose of renally excreted drugs.

Methods

Search strategy, study selection and validation

Relevant publications were identified through electronic searches using PubMed and EMBASE databases up to January 2014. The following keywords 'Pharmacokinetics' AND 'cystatin C' with limitation to 'human' were used.

Studies were eligible if 1) they were pharmacokinetic studies and 2) CysC was used as a marker of renal function. All publications were screened on title, abstract and then full text independently by two investigators.

Data extraction

All data from eligible studies were independently extracted by two investigators using a standardized extraction form with the following information: year of publication and journal, studied patients' characteristics (number of patients, age, weight and clinical condition), analytical method for creatinine (enzymatic or Jaffé method) and CysC, drug analytical method for determination of drug concentration and pharmacokinetic parameters.

Results

The electronic search based on the screening of title and abstract yielded a total of 165 reports from PubMed and 297 from EMBASE. The study screening process is presented in Figure 1. After assessing the full text articles for eligibility, 16 articles were identified. They were published between 2004 and 2014 and conducted in three therapeutic classes: antimicrobials (vancomycin [30–35], amikacin [36], cefuroxime [37] and arbekacin [38]), anti-cancer drugs (topotecan [39], carboplatin) [40] and cardiovascular drug (digoxin [41–43]). Most studies were conducted with vancomycin (44%, n = 7). Corresponding study characteristics are presented in Tables 1–3. All drugs are renally excreted. The percentage of renal clearance ranged from 50% (topotecan) to 96 % (carboplatin) [44–50].

Among these 16 studies, only one study was performed in children [36] and the others were performed in adults and/or elderly patients (>65 years). The particle-enhanced turbidimetric immunoassay (PETIA) (n = 4) and particle-enhanced nephelometric immunoassay (PENIA) (n = 12) were used to measure the serum concentrations of CysC. The Jaffe method (n = 7) and

Table 1

Summary of seven evaluated drugs

Drug class	Drugs	Number of studies	Renal elimination (%)
Antimicrobials	Vancomycin	7	>80
	Arbekacin	1	~50
	Amikacin	1	68–80
	Cefuroxim	1	>90
Anticancer drugs	Carboplatin	2	96
	Topotecan	1	~50
Cardiovascular drug	Digoxin	3	79–83

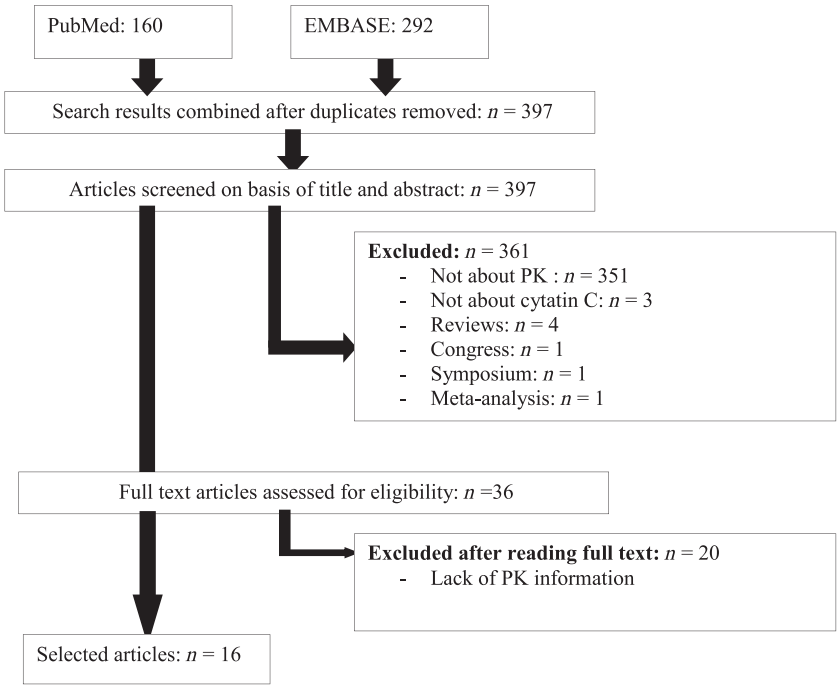

Figure 1

Study screening process

Table 2

Antimicrobial cystatin C pharmacokinetic study

		Population			Analytical methods			Renal function		Renal function-PK		
Drug	Study	Number of patients	Patients	Age range (years)	Creatinine	CysC	Drug	GFR based on creatinine	GFR based on CysC	Significant correlation between CysC and drug clearances (r^2)	Significant correlation between CysC and drug C0 (r^2)	CysC is better correlated with PK compared to creatinine (r^2)
Vancomycin	Chen *et al.* [30]	65	Adult and elderly patients	19–78	Enzymatic	PETIA	FPIA	Creatinine clearance*	Flodin	Yes (0.85)	—	Yes (0.64)
	Tanaka *et al.* [54]	60	Adult patients	16–64	—	PENIA	—	CG¶¶	Hoek ‡	—	Yes (0.78)	Yes (0.54)
		105	Elderly patients	66–95	—	PENIA	—	CG	Hoek	—	Yes (0.79)	Yes (0.18)
	Kees *et al.* [31]	25	Critically ill adults and elderly patients	31–82	Enzymatic	PENIA	HPLC	CG	Hoek	Yes (0.70)	—	Yes (0.37)
	Suzuki *et al.* [32]	18	Adult patients	—	Enzymatic	PENIA	FPIA	CG/ MDRD§	Rules¶/Hoek	—	Yes (0.42/0.49)	Yes (0.13/0.19)
	Tanaka *et al.* [33]	164	Adult and elderly patients	17–95	—	PENIA	FPIA	—	Hoek	Yes (0.84)	—	—
	Okamoto *et al.* [34]	24	Elderly patients	66–87	Enzymatic	PETIA	FPIA	CG	Larsson**	Yes (0.78)	—	Yes (0.47)
	Chung *et al.* [35]	678	Adult and elderly patients	18–96	Jaffé	PETIA	FPIA	CG	Concentration	Yes	—	Yes
Amikacin	Halacova *et al.* [36]	71	Adults and children with cystic fibrosis	4–28	Enzymatic	PETIA	FPIA	CG / Schwatz††	Grubb‡‡/Larsson	Yes	—	Yes
Cefuroxime	Viberg *et al.* [37]	97	Adult patients	24–95	Enzymatic	PENIA	HPLC	Concentration	Concentration	—	Yes	Yes
Arbekacin	Otsuka *et al.* [38]	95	Adult and elderly patients	73–16	Enzymatic	PENIA	FPIA	CG	Sjöström§§	—	Yes (0.89)	Yes (0.64)

CG, Cockcroft–Gault equation; CysC, cystatin C; FPIA, fluorescence polarization immunoassay; HPLC, high-performance liquid chromatography; MDRD, modification of diet in renal disease equation; PENIA, particle-enhanced nephelometric immunoassay; PETIA, particle-enhanced turbidimetric immunoassay. *Creatinine clearance = creatinine concentration in urine x urine flow rate / plasma creatinine concentration. †Flodin equation: eGFR = 79.901 × $CysC^{-1.4389}$. ‡Hoek equation: eGFR = (80.35 / CysC) – 4.32. §MDRD equation: eGFR = 186.3 × (creatinine / 88.4) $^{-1.154}$ × $age^{-0.203}$ × 0.742 (if female) × 1.21 (if African). ¶Rules equation: eGFR = 66.8 × $CysC^{-1,3}$. **Larsson equation: eGFR = 99.43 × $CysC^{-1.5837}$. ††Schwartz equation: eGFR = k × height / serum creatinine; the value of k varies as a function of age and gender being 0.33 in preterm infants, 0.45 in term infants, 0.55 in child or adolescent girls and 0.7 in adolescent boys. ‡‡Grubb equation: eGFR = 84.69 × $CysC^{-1.68}$ × 1.384 (if a child <14 years). §§Sjöström equation eGFR = (124 / CysC) – 22.3. ¶¶Cockroft–Gault: eGFR= k × weight × (140 – age) / creatinine; the value of k is 1.23 for men and 1.04 for women.

Table 3

Cardiovascular and anticancer drugs cystatin C pharmacokinetic study

			Population			Detection method			Renal function		Renal function-PK		
Drug class	Drug	Study	Number of patients	Patients	Age (years)	Creatinine	CysC	Drug	Creatinine	CysC	Significant correlation between CysC and drug clearance (r^2)	Significant correlation between CysC and drug C0 (r^2)	CysC is better correlated with PK compared to creatinine (r^2)
Cardiac drug	Digoxin	Hallberg *et al.* [41]	149	Adult and elderly patients	55–106	Jaffé	PENIA	FPIA	Concentration	Concentration	—	Yes (0.20)	Yes (0.14)
		Garcia *et al.* [42]	61	Adult and elderly patients with cardiac insufficiency	24–92	Jaffé	PENIA	FPIA	CG	Larsson	Yes (0.25)	Yes	Yes (0.16)
		O'Riordan *et al.* [43]	18	Elderly healthy patients	67–86	Jaffé	PENIA	FPIA	Concentration	Concentration	—	No (0.09)	No (0.16)
Anticancer	Carboplatin	Thomas *et al.* [40]	45	Adult and elderly patients with cancer	21–79	Jaffé	PENIA	FAAS	CG	Concentration	Yes	—	Yes
		Schmitt *et al.* [61]	357	Adult and elderly patients with cancer	21–87	Jaffé	PENIA	FAAS	Concentration	Concentration	Yes	—	—
	Topotecan	Hoppe *et al.* [39]	59	Adult and elderly patients with cancer	18–76	Jaffé	PENIA	HPLC	Concentration	Concentration	Yes (0.43)	—	Yes (0.23)

CG, Cockcroft–Gault equation; CysC, cystatin C; FAAS, flameless atomic absorption spectrophotometric analysis; FPIA, fluorescence polarization immunoassay; HPLC, high-performance liquid chromatography; PENIA, particle-enhanced nephelometric immunoassay.

immune-enzymatic method (n = 7) were used to measure serum concentrations of creatinine.

Different equations were used to quantify renal function (Table 2). For creatinine-based formulae, the Cockcroft & Gault (CG) equation (n = 10), modification of diet in renal disease equation (MDRD) (n = 1) or Schwartz formula (n = 1) were used. One study used creatinine clearance determined with serum and urine creatinine concentrations and five studies used only serum creatinine concentration. For CysC-based formulae, Hoek (n = 4), Rules (n = 1), Larsson (n = 3), Foldin (n = 1), Grubb (n = 1) and Söstrom (n = 1) formulae were used. Seven studies used directly serum CysC concentrations.

The reported correlations between renal function (determined with the different biomarkers and formulae) and clearance of renal excreted drugs were then analyzed. As demonstrated in Table 2 for pharmacokinetic studies of antimicrobials, CysC was significantly correlated with the clearance/trough concentration of vancomycin (n = 7), amikacin (n = 1), cefuroxime (n = 1) and arbekacin (n = 1). In Table 3, the pharmacokinetic studies of anticancer and cardiovascular drugs, CysC was significantly correlated with carboplatin (n = 2) and topotecan (n = 1) clearance. For digoxin studies (n = 3), two studies showed that CysC was significantly correlated with digoxin clearance/trough concentration, but one study found that neither CysC nor creatinine was significantly correlated with digoxin trough concentration. Among all the 16 published studies, 15 studies demonstrated the significant impact of CysC on clearance/trough concentration of evaluated drugs, except for one study conducted in elderly patients (see Table 3).

In addition, 14 studies compared directly the impact of CysC and creatinine clearance on drug elimination. Thirteen of them showed that CysC was superior to creatinine to predict elimination of the evaluated drug.

Discussion

There is a need to optimize the evaluation of renal function, as it remains a central factor to predict accurately the dose of renally excreted drugs. Both creatinine and CysC are available in clinical practice as biomarkers, but creatinine determination is used in most cases. In the present work, 16 pharmacokinetic studies identified in the literature were used to compare two biomarkers of renal function. The comparison was based on different formulae to quantify GFR with creatinine or CysC, showing CysC was a better predictor of the elimination of predominantly renally excreted drugs.

Creatinine is produced from creatine, which is a component of muscle. It is filtered and secreted by proximal renal tubules. The calculated creatinine clearance values are known to overestimate GFR, in particular for patients with decreased renal function [3–6]. In addition, for some special patients groups, such as neonates, the influence of residual maternal creatinine and interference with endogenous compounds and drugs used in sick patients (such as ketoacids, bilirubin, cephalosporins) may lead to inaccuracies in predicting GFR [7, 8]. CysC is freely filtered through the renal glomerulus and subsequently reabsorbed and catabolized in proximal renal tubules [23–25]. CysC is a potential alternative marker to creatinine, as it is not affected by age, gender, diet or inflammation, making it an ideal endogenous marker of renal function [51, 52].

Importantly, the consistent results were found in elderly patients. Renal function has a profound impact on dosage adjustment in this special population, as it is well known that drug elimination through the kidneys is impaired, due to reduced renal blood flow and GFR [53]. Our results supported that CysC was well correlated with the elimination of renally excrelly drugs. This was in agreement with previous findings, showing that CysC was more precise to predict GFR than the creatinine-based Cockcroft–Gault equation in elderly patients [54]. Only one study was conducted in children, showing that amikacin clearance was better correlated with CysC than serum creatinine [36]. In addition, Neamatollah *et al*. also showed that CysC was more sensitive to detect acute kidney injury in critically ill children than creatinine [55]. Given that renal maturation has a major impact in children, further studies are required to confirm the role of CysC to predict the dose of renally excreted drugs in this vulnerable population.

The underlying disease and mechanisms of renal impairment were variable in the present analysis, as the studies were conducted in healthy volunteers, cystic fibrosis and cancer patients. In patients with cystic fibrosis, amikacin clearance was better correlated with CysC than creatinine [36]. These results are in accordance with the findings by Beringer *et al.* [56] who reported that the CysC formula demonstrated greater sensitivity and specificity to quantify GFR in cystic fibrosis patients compared with the equations with serum creatinine (Cockcroft–Gault; MDRD). For cancer patients, carboplatin and topotecan clearances were better correlated with CysC than creatinine clearance, in accordance with the findings of Barnfield *et al*. [57]. Discordances were reported with digoxin [41–43. O'Riordan *et al.* reported that neither CysC nor creatinine was significantly correlated with digoxin trough concentration. This is probably related to the low number of patients (n = 18) and the limited alteration of renal function (serum CysC values of 0.7 to1.9 mg l^{-1}, serum creatinine values of 70 – 154 μmol l^{-1}).

According to differences between these markers in terms of renal handling, analytical methods, impact of physiological factors and origin of the formulae used, differences in the quantification of renal function are expected. Indeed, there is no clear consensus on the best CysC-based equation to predict the individual dose of a

renally eliminated drug. Tanaka *et al*. showed that the Hoek formula was more accurate than the Grubb, Sjostrom, and Larson's formulae to predict vancomycin clearance and GFR [58]. However, using arbekacin as test drug, Otsuka *et al*. reported that the Sjostrom equation was more accurate for determining the initial drug dose than the Hoek and Grubb equations in a Japanese population [38].

The impact of biomarker analytical methods on pharmacokinetics should also be analyzed carefully. Recently, we have reported that vancomycin population pharmacokinetic models in neonates cannot be transferred from the initial to different clinical settings because of inter-centre differences in the laboratory methods to measure serum creatinine [59]. The same caution should be taken into consideration to interpret serum CysC concentrations, as analytical methods (namely PENIA, PETIA and ELISA) are used indifferently. It was proposed that CysC ELISA values required normalization by a factor 0.66 to correct the difference with PENIA and PETIA methods [60], although additional data are required for validation.

Conclusion

Our review supports that CysC is a good marker of renal function and can be used to adjust the dose of renally eliminated drugs in adult and elderly patients. Efforts should be made to evaluate the impact of CysC in special populations (e.g. paediatrics, critically ill patients), as renal function fluctuates considerably and a sensitive biomarker is required for dosage optimisation in these patients.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare this work was supported by the GRIP (Global Research in Paediatrics, European Commission FP7 project, grant agreement number 261060) and 'The Fundamental Research Funds of Shandong University', no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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