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Clinical Investigation

Prediction of Warfarin Dose in Pediatric Patients: An Evaluation of the Predictive Performance of Several Models

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OBJECTIVES: The objective of this study was to evaluate the performance of pediatric pharmacogenetic-based dose prediction models by using an independent cohort of pediatric patients from a multicenter trial.
METHODS: Clinical and genetic data (CYP2C9 [cytochrome P450 2C9] and VKORC1 [vitamin K epoxide reductase]) were collected from pediatric patients aged 3 months to 17 years who were receiving warfarin as part of standard care at 3 separate clinical sites. The accuracy of 8 previously published pediatric pharmacogenetic-based dose models was evaluated in the validation cohort by comparing predicted maintenance doses to actual stable warfarin doses. The predictive ability was assessed by using the proportion of variance (R^2), mean prediction error (MPE), and the percentage of predictions that fell within 20% of the actual maintenance dose.
RESULTS: Thirty-two children reached a stable international normalized ratio and were included in the validation cohort. The pharmacogenetic-based warfarin dose models showed a proportion of variance ranging from 35% to 78% and an MPE ranging from −2.67 to 0.85 mg/day in the validation cohort. Overall, the model developed by Hamberg et al showed the best performance in the validation cohort (R^2 = 78%; MPE = 0.15 mg/day) with 38% of the predictions falling within 20% of observed doses.
CONCLUSIONS: Pharmacogenetic-based algorithms provide better predictions than a fixed-dose approach, although an optimal dose algorithm has not yet been developed.

INDEX TERMS: children, pediatrics, pharmacogenetics, warfarin

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INTRODUCTION

Warfarin is the most commonly prescribed oral anticoagulant in infants and children. It is often used off-label for prophylaxis after Fontan surgery, mechanical prosthetic valves, Kawasaki disease with large aneurysms, dilated cardiomyopathy, and idiopathic pulmonary arterial hypertension.[1] Management of warfarin therapy in adults is complicated by its narrow therapeutic window and variability in warfarin disposition and response among and between patients. In infants and children, warfarin use is further complicated by diet variations, frequent illnesses, and dynamic and developing hepatic and hemostatic systems.

Polymorphisms in the cytochrome P450 2C9 *(CYP2C9)* and vitamin K epoxide reductase *(VKORC1)* genes have been shown to account for approximately 6% to 45% of adult warfarin dose variation depending on the patient population studied.[2] CYP2C9 is responsible for the metabolism of the more pharmacologically active S-enantiomer of warfarin and the *CYP2C9*2* and

*CYP2C9*3* allelic variants have been associated with smaller therapeutic doses.[3,4] VKORC1 recycles reduced vitamin K, and gene polymorphisms, including rs9923231 (–1639 G>A), confer increased warfarin sensitivity, necessitating smaller therapeutic doses.[5,6] The efficacy and safety of warfarin therapy are dependent on maintaining the international normalized ratio (INR) within a target range. For example, a retrospective review of adult venous thromboembolism patients showed that patients with an INR < 2.0 had a higher incidence of thromboembolism (relative risk [RR] 4.5, 95% confidence interval [CI] 3.1-6.6), while patients with an INR > 5.0 had a higher incidence of major bleeding (RR 6.4, 95% CI 2.5-16.1) than patients with an INR of 2.0 to 3.0.[7]

Although smaller in size than the published adult studies, several recent pediatric studies[8-13] have suggested that *CYP2C9* and *VKORC1* allelic variation may account for approximately 4% to 50% of warfarin dose variability, and several pediatric pharmacogenetic-based prediction models[8-15] have been developed in an attempt to explain the interindividual variability in warfarin response. Although genetic variation has been associated with warfarin response, the clinical utility of these dose algorithms remains controversial. External validation using an independent data set is critical to providing predictive information and thereby help guide future clinical decisions. Therefore, the objective of the current study was to externally validate and compare the accuracy of dose predictions in published pediatric pharmacogenetic-based prediction models with a cohort of warfarin-treated children from a US Food and Drug Administration (FDA)–sponsored multicenter trial.

MATERIALS AND METHODS

Clinical Protocol

Patients were recruited from 3 US medical centers: Children's Mercy Kansas City, Children's Hospital of Los Angeles, and Children's Hospital of Wisconsin. The study was approved by the FDA's Research Involving Human Subjects Committee and the local ethics committees of all participating institutions. Patients 3 months to 17 years of age who were currently receiving warfarin or who had received warfarin treatment for greater than 7 days within the past year were eligible for study inclusion. Patients and/or parents were fully informed about the study and, when appropriate, patient assent was obtained. Information on age, weight, height, sex, warfarin dose, INR, prothrombin time, other medical illness or medications, and adverse drug reactions was collected for all patients. Indications for warfarin were classified as follows: thrombosis, congenital heart disease, prosthetic heart valve, and "other" for remaining indications. Target INR varied according to indication. A stable INR was defined as 3 consecutive INRs at least a week apart with no change in warfarin dose and an INR within 10% of the predetermined target range.

Genotyping

Whole blood was collected from all patients into EDTA-vacutainers and DNA was extracted by using a QIAmp DNA Blood Mini Kit (Qiagen, Valencia, CA). DNA quality was asserted via agarose gel electrophoresis and concentration determined spectrophotometrically with a NanoDrop 2000 (NanoDrop Products, Wilmington, DE). Six single nucleotide polymorphisms (SNPs) of *CYP2C9* were assayed to determine the presence of the following allelic variants: *CYP2C9*2* (rs1799853), **3* (rs1057910), **5* (rs28371686), **6* (rs9332131), **8* (rs7900194), and **11* (rs28371685). In the absence of any of these SNPs, a *CYP2C9*1/*1* genotype was assigned. Allele designations are per the Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se/). For *VKORC1*, rs9923231 (-1639 G>A) was interrogated. Genotyping was performed by using commercially available TaqMan genotype assays (Thermo Fisher Scientific, formerly Life Technologies, Foster City, CA). Briefly, 6-µL reactions were carried out in 96-well plates by using the KAPA Probe qPCR Master Mix (KAPA Biosystems, Wilmington, MA). Cycling was performed on the Applied Biosystems 7900 Real Time PCR System (Applied Biosystems, Waltham, MA) according to manufacturer's specifications. Data were analyzed with the SDS2.4 software.

Statistical Analysis

Patient demographics were analyzed by using descriptive statistics including median and range values. The individual predicted daily dose was compared to the mean observed individual daily dose. From the individual predicted and

observed dose values, the mean prediction error was calculated with the following equation:

$$\text{MPE} = \frac{1}{n}\sum \text{OBSij} - \text{PREDij}$$

The mean prediction error (MPE) was defined as the average of differences between the observed warfarin doses and the predicted doses and is a measure of bias.

Model Comparison

The performance of 8 pediatric pharmacogenetic-based dose models, including 2 pharmacokinetic/pharmacodynamic (PK/PD) models[14,15] and 6 linear regression models,[8-13] were evaluated by using the validation cohort. The empiric standard warfarin body-weight dose was assumed to be 0.2 mg/kg/day.[16] Specific model covariates are shown in Table 1. Demographics, clinical characteristics, and genetics used in model derivation/development are shown in Table 2. The output from each model was converted to a daily dose and compared to the actual daily maintenance dose. To determine the ability of the models to explain variability in maintenance dose requirements, the predicted warfarin dose was plotted against the actual warfarin maintenance dose. The accuracy of each model was assessed by using the R^2 (proportion of variance) statistic and MPE. Clinical accuracy of the predictions was assessed by calculating the proportion of patients in which the predicted dose was 20% or more below the actual dose (underdosed), within 20% of the actual dose (ideal dose), or 20% or greater above the actual dose (overdosed).

The validation cohort was classified as requiring an INR goal range of 1.5 to 3.3 (n = 13), 1.8 to 3.2 (n = 10), or 2.5 to 4 (n = 9) accordingly to the Moreau model.[10] The predicted warfarin dose for the Hamberg PK/PD model was estimated on the basis of the published Warfarin Dose Calculator 1.0.1 by using the *a priori* estimated dose function.[17] The predicted warfarin dose for the Lala PK/PD model was estimated by using the optimized starting dose from Table 2 of the original article.[14]

RESULTS

Patient Characteristics

A total of 48 children were enrolled and genotyped between 2008 and 2013. Thirty-two children reached a stable INR and were included in the validation cohort. Sixteen children never achieved a stable dose after a median follow-up of 215 days and were excluded from the analysis. Characteristics of the validation cohort are displayed in Table 3. The median age was 4 years and 9 months and the median weight was 16.1 kg at the time of the stable dose. Most patients (n = 31) were white. The most common indications for warfarin treatment were congenital heart disease (n = 11) or a prosthetic heart valve (n = 11). Eleven children (34%) had Fontan procedures. The median time to reach a stable INR as defined by the study was 95 days, with maintenance doses ranging from 0.7 to 10 mg/day. Genotype frequencies for *VKORC1* -1639 G>A, *CYP2C9*2* and **3* were similar to those previously reported.[18-20] We did not observe *CYP2C9*5, *6, *8*, or **11* in our patient cohort. None of the children experienced a clinically significant bleed.

Model Comparison

Comparisons of dose predictions in the study cohort are summarized in Table 4. Pharmacogenetic-based algorithms provided dose estimates that were closer to actual dose requirements than estimates derived from a fixed-dose approach, as evidenced by lower mean prediction errors. The pharmacogenetic warfarin dose models showed a proportion of variance (R^2) ranging from 35% to 78%. The Hamberg[21] and Nguyen[11] models showed the highest correlation with R^2 values of 78% and 74%, respectively. Bias (MPE) was smallest for the predictions made by the Nowak-Gottl[8] and Hamberg[21] models (−0.03 and 0.15, respectively). Besides the Lala[15] and Hamberg[21] model, all of the other models tended to overpredict warfarin maintenance doses. The pharmacogenetic warfarin dose models predicted an ideal maintenance dose (±20%) in 9% to 47% of patients. Overall, the Hamberg[21] and Moreau[10] models had the best predictive performance (R^2 = 78%; MPE = 0.15 mg/day; 38% within 20% of the ideal dose range and R^2 = 66%; MPE = −0.19 mg/day; 47% within 20% of the ideal dose range, respectively) in this cohort of patients.

DISCUSSION

The objective of this study was to validate previously published pharmacogenetic-based warfarin models with an independent cohort of

Table 1. Published Genotype-Based Warfarin Dose Algorithm Covariates

Model	Reference	Derivation	Dose Prediction Units	*VKORC1* Genotype	*CYP2C9* Genotype	Weight	Age	Height	Indication	INR Goal
a	Nowak-Gottl et al[8]	Linear regression	mg/kg/day	X	X		X			
b	Biss et al[9]	Linear regression	mg/day	X	X			X	X	
c	Moreau et al[10]	Linear regression	mg/wk	X	X			X		X
d	Nguyen et al[11]	Linear regression	mg/kg/day	X	X		X			X
e	Hamberg et al[17,21]	PK/PD	mg/day	X	X	X	X			X
f	Lala et al[15]	PK/PD	mg/kg/day	X	X	X*	X			
g	Shaw et al[13]	Linear regression	mg/day	X	X	X			X	
h	Vear et al[12]	Linear regression	mg/day	X	X		X			

CYP, cytochrome P450; INR, international normalized ratio; PK/PD, pharmacokinetic/pharmacodynamic; VKORC1, vitamin K epoxide reductase

a: $\sqrt{\text{Dose (mg/kg/day)}} = 0.49 - 0.013 \times \text{Age (yr)} - 0.08$ (VKORC1A/A) + 0.01 (VKORC1A/G) – 0.02 (if not CYP2C9 wild type)

b: $\sqrt{\text{Dose (mg/day)}} = -0.009 + 0.11 \times \text{Height (cm)} + 0.357 \times$ VKORC1 (0 for A/A, 1 for A/G, 2 for G/G) – 0.478 × CYP2C9 * 3 (number of CYP2C9 * 3 alleles) – 0.277 × CYP2C9 *2 (number of CYP2C9 * 2 alleles) + 0.186 × Indication (0 for Fontan procedure, 1 for other)

c: Dose (mg/wk) = −10.77 + 0.28 × Height (cm) – 5.4 × VKORC1 (0 for G/G, 1 for A/G, 2 for A/A) + 7.83 (if target INR 2.5) + 11.52 (if target INR 3.3) – 3.29 × CYP2CP (number of CYP2C9 * 2 or * 3 variant alleles), categorize INR goals into 3 prespecified INR ranges

d: Dose (mg/kg/day) = −0.09 – 0.0006 × Age (yr) + 0.11 (if VKORC1 C/C) + 0.043 (if VKORC1 C/T) + 0.045 (if CYP2C9 * 1/*1) + 0.039 (if CYP2C9*1/*2) + 0.073 × Target INR

e: Warfarin Dose Calculator 1.0.1 a priori estimated dose

f: Table 2

g: $\sqrt{\text{Dose (mg/day)}} = 1.711 + 0.014 \times \text{Weight (kg)} - 0.257 \times$ VKORC1 (0 for G/G, 1 for A/G, 2 for A/A) – 0.127 × CYP2C9 * 2 (number of variant alleles) – 0.463 × CYP2C9 * 3 (number of variant alleles) – 0.161 × Indication (1 for Fontan procedure, 0 for other)

h: Log Dose (mg/day) = 1.098 + 0.027 × Age (yr) – 1.124 (VKORC1 A/A) – 0.733 (VKORC1 G/A) + 0.345 (CYP2C9 * 1/(*1)) + 0.031 (Age × VKORC1 A/A) + 0.037 (Age × VKORC1 G/A)

* Two different mg/kg doses for smaller (<20 kg) or larger (≥20 kg) subjects within each genotype category

Table 2. Demographic, Clinical, and Pharmacogenetic Information for Derivation of Models

Reference	N	Median Age (Range), yr	Ethnicity	Observed Dose (mg/kg/day)	VKORC1 Status, n (%)			CYP2C9 Status, n (%)			
					GG	GA	AA		*1	*2	*3
Nowak-Gottl et al[8]	59 (34 on warfarin)	15.0 (1.0-19.0)	100% white	0.03-0.6	27 (46)	25 (42)	7 (12)	*1	39 (66)	11 (19)	8 (14)
								*2		1 (2)	0
								*3			0
Biss et al[9]	120	11 (1-18)	76% white, 24% other	0.5-12.5†	43 (36)	55 (46)	22 (18)	*1	84 (70)	17 (14)	17 (14)
								*2		1 (1)	1 (1)
								*3			0
Moreau et al[10]	118 (83 on warfarin)	8.4* (0.25-18)	>90% white	0.03-0.50	25 (30)	43 (52)	15 (18)	*1	53 (64)	‡	‡
								*2		‡	‡
								*3			‡
Nguyen et al[11]	37	9.6* (1.8-18.6)	73% white, 19% African American, 8% Asian	0.04-0.34	10 (27)	17 (46)	10 (27)	*1	27 (73)	7 (19)	1 (8)
								*2		0	0
								*3			0
Hamberg et al[17,21]#	163	6.3 (0.06-18.9)	77% white, 7% Asian, 16% Other	0.02-0.58	57 (35)	79 (50)	27 (15)	*1	116 (71)	20 (12)	23 (14)
								*2		2 (1)	2 (1)
								*3			0
Lala et al[15]#	26	4.4* (0.33-18)	61% Hispanic, 27% Caucasian, 8% African American, 4% mixed	0.04-0.3	7 (27)	8 (31)	11 (42)	*1	22 (85)	4 (15)	0
								*2		0	0
								*3			0
Shaw et al[13]	93	4.8 (0.17-17.8)	66% European, 17% Asian, 17% other	0.75-10†	39 (42)	37 (40)	17 (18)	*1	65 (70)	14 (15)	12 (13)
								*2		2 (13)	0
								*3			0
Vear et al[12]	100	12.4 (1.0-19.8)	85% white, 8% African American, 7% other	Mean of 4.29†	32 (32)	54 (54)	10 (10)	*1	67 (67)	16 (16)	9 (9)
								*2		0	1 (1)
								*3			0

CYP, cytochrome P450; VKORC1, vitamin K epoxide reductase

* Mean

† mg/day

‡ CYP2C9 status: 25 (30) *2 or *3 heterozygous and 5 (6) *2 or *3 homozygous

Cohorts used to optimize model

Table 3. Characteristics of Cohort (n = 32)

Characteristic	Median (Range) or No. (%)
Age (yr)	4.8 (1.1-17)
Weight (kg)	16.1 (8.4-99.6)
Height (cm)	103.7 (69.5-186.1)
Body surface area (m^2)	0.68 (0.40-2.27)
Sex	
Male	22 (69)
Female	10 (31)
Race	
Multiple races	1 (3)
White	31 (97)
Ethnicity	
Latino or Hispanic	10 (31)
Not Latino or Hispanic	21 (66)
Unknown	1 (3)
Warfarin	
Maintenance dose (mg/day)	2.5 (0.7-10)
Maintenance dose (mg/kg/day)	0.11 (0.02-0.37)
Treatment indication	
Thrombosis	6 (19)
Congenital heart disease	11 (34)
Prosthetic heart valve	11 (34)
Other	4 (13)
INR goal	
1.5-2.5	8 (25)
2-3	9 (28)
2.5-3.5	8 (25)
Other	7 (22)
CYP2C9 genotype	
*1/*1	25 (78)
*1/*2	4 (13)
*1/*3	3 (9)
*2/*2, *2/*3, *3/*3	0 (0)
VKORC1 rs9923231 genotype	
GG	15 (47)
GA	11 (34)
AA	6 (19)

CYP, cytochrome P450; INR, international normalized ratio; VKORC1, vitamin K epoxide reductase

pediatric patients from a multicenter trial. We identified 8 pediatric warfarin dose algorithms that included pharmacogenetic information. All of the pharmacogenetic-based models performed better than a fixed-dose approach. Comparing the pharmacogenetic models, those proposed by Hamberg[21] and Moreau[10] had the best performance in this cohort of patients, although greater than 50% of patients had either underdose or overdose predictions. Both the Hamberg and Moreau models included INR target ranges as a covariate, which may have contributed to their predictive ability in this cohort. Factors such as adherence, drug-drug interactions, and dietary intake of vitamin K, along with other genetic variation, may have contributed to residual unexplained variability in warfarin dose and therefore limit the predictive performance of these models.

Table 4. Accuracy Measures of Warfarin Dose Models

Model	R^2	Mean Prediction Error (95% CI), mg/day	Underpredicted (%)	Ideal (%)	Overpredicted (%)
Fixed dose (0.2 mg/kg/day)	0.33	−3.49 (−5.19, −1.79)	9	9	81
Nowak-Gottl et al[8]	0.52	−0.03 (−0.61, 0.55)	34	16	50
Biss et al[9]	0.66	−0.28 (−0.76, 0.20)	22	37	41
Moreau et al[10]	0.66	−0.19 (−0.67, 0.29)	9	47	44
Nguyen et al[11]	0.74	−2.67 (−3.79, −1.55)	6	19	75
Hamberg et al[17,21]	0.78	0.15 (−0.23, 0.53)	34	38	28
Lala et al[15]	0.60	0.85 (0.34, 1.37)	56	19	25
Shaw et al[13]	0.58	−0.48 (−1.00, 0.05)	16	41	44
Vear et al[12]	0.35	−0.63 (−1.28, 0.03)	16	34	50

CI, confidence interval

These results are in line with those of Hamberg and colleagues,[14,21] where investigators tested the predictive performance of pediatric genotype-based dose algorithms by using a subset of a published pediatric data set. Authors compared 2 PK/PD and 4 linear regression models, determining that the PK/PD model by Hamberg gave the most accurate dose predictions.[21] The PK/PD models show promise with dose predictions and offer more flexibility than linear regression models but often require specialized software for individualized dose predictions. Thus, Hamberg and colleagues[17] created a Java-based tool to estimate individualized *a priori* and *a posteriori* dose predictions. This tool provides universal access to individualized dose predictions and could help overcome specialized software requirements in the future. These PK/PD models are based on the assumption of a similar concentration-response relationship for pediatric and adult patients. Recent research indicates that the concentrations of several coagulation factors, including vitamin K–dependent factors, differ between adults and children from infancy,[22,23] suggesting a potential difference in response to anticoagulants.

External validation is critical for determining the best model for warfarin dose predictions and generating unbiased estimates of model performance. To our knowledge, this is the second report of external validation using an independent cohort of children. In comparison, several adult dose prediction models have undergone external validation.[5,24] In adults, incorporation of genetic and clinical information has been shown to be predictive of stable warfarin dose, but clinical trials evaluating genotype-guided warfarin dose produced mixed results.[25]

This study is limited by its small size and a rather genetically homogenous patient population. We did not have any children with *CYP2C9*2/*2*, *CYP2C9*2/*3*, or *CYP2C9*3/*3* genotypes conferring considerable reduction of CYP2C9 activity, limiting the analysis. In comparing the published genotype-based algorithms, we made a number of assumptions and model performance may have improved with additional patient information. In addition, the American College of Chest Physicians (ACCP) CHEST guideline starting dose of 0.2 mg/kg is intended as a starting dose rather than a daily maintenance dose. However, despite these limitations, the current cohort of warfarin-treated children provides valuable information on the performance of previously published pediatric pharmacogenomics-based warfarin dose models.

Owing to limited patient numbers and challenges in pediatric enrollment in these clinical trials, there is an effort to create a consortium and pool data in order to improve warfarin use in children. Although warfarin is the standard oral anticoagulant used in pediatric patients, prospective randomized controlled trials investigating its use are lacking[1] and there is limited evidence-based information on whom to treat, at what intensity, and the length of treatment.[26] Many of the current recommendations have been extrapolated from adult studies, including indication-related target INRs. According to the ACCP CHEST guidelines, evidence supporting the recommendations for antithrombotic therapy

in neonates and children is weak, and studies addressing appropriate drug target ranges are urgently required.[16] Thus, a consortium could aid in addressing these gaps in our knowledge as well as in investigating the influence of genotype on warfarin dose and response.

CONCLUSION

Genetic testing to guide warfarin therapy in children has not been recommended owing to a lack of evidence,[27] but recent studies have shown a substantial contribution of age-dependent factors and *CYP2C9* and *VKORC1* genotype on dose requirements. Pharmacogenetic-based algorithms provide better predictions than a fixed-dose approach although an optimal dose algorithm has not yet been developed.

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Disclaimer The opinions expressed in this manuscript are those of the authors, and should not be considered to be the position of the US Food and Drug Administration.

Abbreviations ACCP, American College of Chest Physicians; CYP, cytochrome P450; EDTA, ethylenediaminetetraacetic acid; FDA, US Food and Drug Administration; INR, international normalized ratio; MPE, mean prediction error; OBS, observed; PK/PD, pharmacokinetic/pharmacodynamic; PRED, predicted; SNPs, single nucleotide polymorphisms; VKORC1, vitamin K epoxide reductase

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