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Original article

Factors involved in phenoconversion of CYP3A using 4β-hydroxycholesterol in stable kidney transplant recipients

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ABSTRACT

Background: Phenoconversion is a phenomenon whereby some genotypic extensive metabolizers transiently exhibit drug metabolizing enzyme activity at similar level as that of poor metabolizers. Renal failure is known to decrease CYP3A activity in humans. Indoxyl sulfate, parathyroid hormone (PTH), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) have been reported to cause CYP3A downregulation in renal failure. We measured plasma concentrations of the above compounds in stable kidney transplant recipients, and evaluated their relations with phenoconversion of CYP3A evaluated by plasma concentration of 4β-hydroxycholesterol, a biomarker of CYP3A activity. Phenoconversion was defined as a genotypic extensive/intermediate metabolizer exhibiting CYP3A activity below the cutoff value that discriminates extensive/intermediate from poor metabolizers.

Methods: Sixty-three Japanese kidney transplant recipients who underwent transplantation more than 180 days prior to the study were included. Morning blood samples were collected, and CYP3A5 polymorphism as well as plasma concentrations of 4β-hydroxycholesterol, indoxyl sulfate, intact-PTH, IL-6 and TNF-α were determined.

Results: Significantly higher plasma 4β-hydroxycholesterol concentration was observed in recipients with *CYP3A5*1* allele (n = 23) compared to those without the allele (n = 40), and the cut-off value was 40.0 ng/mL. Ten recipients with *CYP3A5*1* allele exhibited CYP3A activity below 40.0 ng/mL (phenoconversion). Only plasma indoxyl sulfate concentration was significantly higher in recipients with CYP3A phenoconversion compared to those without phenoconversion.

Conclusions: These findings suggest that higher plasma indoxyl sulfate concentration may be involved in CYP3A phenoconversion. Dose adjustment of drugs metabolized by CYP3A may be needed in patients with *CYP3A5*1* allele and high blood indoxyl sulfate.

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Introduction

Cytochrome P450 (CYP)3A is the most important enzyme involved in the metabolism of 30–40% of currently prescribed drugs [1]. The expression level and activity of CYP3A show large intra- and inter-individual variability, which contributes to unpredictable drug response and toxicity. A multitude of environmental, physiologic, and genetic factors have been reported to influence the variability of CYP3A expression and activity [2]. CYP3A5 exhibits genetic polymorphisms, and the most common loss-of-function variant is designated *CYP3A5*3* (rs776746, 6986 A > G) [3]. People homozygous for the *CYP3A5*3* allele (poor metabolizers) show lower clearance of CYP3A5 substrates such as tacrolimus [4], cilostazol [5], and verapamil [6] than people heterozygous (intermediate metabolizers) or homozygous for the *CYP3A5*1* allele (extensive metabolizers). However, some extensive metabolizers transiently exhibit similar level of CYP3A activity as in poor metabolizers, although they should have higher metabolic capacity genetically. This phenomenon, in which a genotypic extensive metabolizer is converted transiently to phenotypic poor metabolizer, is called

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phenoconversion [7]. Phenoconversion has been reported for several drug metabolizing enzymes. Phenoconversion of CYP2D6 is most commonly reported in patients with various diseases such as human immunodeficiency virus infection [8,9], chronic hepatitis C virus infection [10], and depression [11]. Especially, the largest scale study reported by Preskorn et al. [11] showed phenoconversion of CYP2D6 in 24% of patients with depression. Phenoconversion was also reported for CYP2C19, and 25%–37% of genotypic extensive metabolizers exhibited poor metabolizer phenotype [12–14]. On the other hand, to the best of our knowledge, whether phenoconversion of CYP3A occurs in patients remains unknown.

Renal failure is known to decrease CYP3A activity in humans [15]. Some uremic toxins, parathyroid hormone (PTH), and inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been reported to induce downregulation of CYP3A in renal failure, in both *in vitro* [16–22] and *in vivo* experiments [19]. Recently, we reported that accumulation of indoxyl sulfate, a uremic toxin, was involved in the decrease in CYP3A activity in patients with chronic renal failure [23], although the clinical effects of PTH, IL-6 and TNF-α in humans are unknown. These substances have the potential to be involved in phenoconversion of CYP3A in patients with chronic renal failure. Based on this hypothesis, we determined CYP3A5 polymorphism in stable kidney transplant recipients, and measured plasma concentrations of indoxyl sulfate, PTH, IL-6 and TNF-α and evaluated their relations with CYP3A phenoconversion evaluated by plasma concentration of 4β-hydroxycholesterol, a biomarker of CYP3A activity. In this cross-sectional study, we defined CYP3A phenoconversion as a genotypic extensive/intermediate metabolizer (with *CYP3A5*1* allele) exhibiting CYP3A activity below the cutoff value that discriminates between extensive/intermediate (with *CYP3A5*1* allele) and poor metabolizers (without *CYP3A5*1* allele).

Materials and methods

Patients

Sixty-three Japanese kidney transplant recipients who underwent transplantation more than 180 days prior to the study were included between November 2014 and November 2016. No recipients required dialysis at the time of study. Fifty-five recipients were treated with tacrolimus and 8 recipients with cyclosporine A. In addition, methylprednisolone, mycophenolate mofetil, mizoribine and everolimus were given concomitantly in 59, 39, 24 and 12 recipients, respectively. No recipient received medications that are inhibitors or inducers of CYP3A [24] within 3 months before the study. Morning blood samples were collected and centrifuged, and plasma samples were frozen at −40 °C. The following clinical data were collected: gender; age; body weight; prescribed drugs; and laboratory data including white blood cell count, C-reactive protein, total cholesterol, alanine aminotransferase (ALT), total bilirubin, and serum creatinine. No recipients were hemodialyzed. Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for Japanese [25]. This study was approved by the ethics committee of Oita University (approval number: 567). Each recipient received information about the scientific purpose of the study and gave written informed consent.

Determination of CYP3A5 genotype

DNA was prepared from venous blood sample using the Maxwell® 16 DNA Purification Kit (Promega, Tokyo, Japan). All samples were analyzed for the single nucleotide polymorphism A6986 G (*CYP3A5*3*). Allelic discrimination reaction was performed using TaqMan genotyping assays (C_26201809_30) in a LightCycler® Nano System (Roche Applied Science, Penzberg, Germany). When the *CYP3A5*3* allele was not detected, the test allele was designated *CYP3A5*1*.

Measurements of plasma concentrations of 4β-hydroxycholesterol, indoxyl sulfate, intact-PTH, IL-6 and TNF-α

Plasma concentrations of 4β-hydroxycholesterol were measured using a gas chromatography/mass spectrometry according to the procedures which we reported previously [26]. Inter-assay and intra-assay coefficients of variation were < 4.7%. Plasma indoxyl sulfate concentrations were determined using high-performance liquid chromatography according to the procedures we reported previously [23]. Inter-assay and intra-assay coefficients of variation were < 5.8%. Plasma intact-PTH concentrations were measured by an electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). Plasma IL-6 and TNF-α concentrations were determined using commercially available enzyme-linked immuno-sorbent assay kits (Human IL-6 and TNF-alpha Quantikine HS ELISA Kit, R&D Systems, Minneapolis, USA).

Data analysis and statistics

Data are expressed as mean ± standard deviation (S.D.). The cut-off value of plasma 4β-hydroxycholesterol concentration to discriminate between the presence or absence of CYP3A phenoconversion was determined using classification and regression tree (CART) analysis. Differences and 95% confidence interval (CI) of differences between recipients with and those without phenoconversion of CYP3A were compared using Fisher's exact test, two-sided Student's *t* test, Welch's *t* test, or Mann–Whitney U test. A *p* value less than 0.05 was considered statistically significant and statistical analyses were performed using the R software version 3.3.1 (http://www.r-project.org) and the Predictive Analysis Software (PASW) Statistics version 23.0 (SPSS Inc., IL, USA).

Results

Table 1 shows the clinical data of the 63 recipients. They comprised 23 recipients with *CYP3A5*1* allele (*CYP3A5*1/*1* or **1/*3*) and 40 recipients without *CYP3A5*1* allele (*CYP3A5*3/*3*). Plasma concentration (mean ± SD) of 4β-hydroxycholesterol was 36.4 ± 11.7 ng/mL; indoxyl sulfate was 12.0 ± 11.8 μM, and intact-PTH, IL-6 and TNF-α were 151.9 ± 141.8, 1.9 ± 1.7 and 2.1 ± 2.1 pg/mL, respectively. Large inter-individual variations were observed in all the parameters measured.

Table 1
Characteristics of kidney transplant recipients in the study.

Characteristic	Value
No. of patients	63
Males / females	43/20
Age (year)	49.5 ± 13.5 [19–77]
Body weight (kg)	59.5 ± 13.3 [39.1–98.0]
Elapsed time after transplantation (day)	1410.2 ± 1385.9 [181–7076]
White blood cell count (/μL)	6427 ± 1999 [2330–13270]
Total cholesterol (mg/dL)	197.3 ± 38.3 [124–334]
ALT (IU/L)	17.3 ± 13.7 [3.1–101.7]
Total bilirubin (mg/dL)	0.65 ± 0.21 [0.23–1.16]
eGFR (mL/min/1.73 m^2)	37.0 ± 13.5 [8.5–67.0]
CYP3A5 polymorphism	
*CYP3A5*1/*1*	4
*CYP3A5*1/*3*	19
*CYP3A5*3/*3*	40

ALT, alanine aminotransaminase; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate. Data are expressed as number of subjects, or mean ± standard deviation [range].

When recipients were divided by CYP3A5 polymorphism into two groups, significantly higher plasma 4β-hydroxycholesterol concentration was observed in recipients with *CYP3A5*1* allele (n = 23) compared to those without *CYP3A5*1* allele (n = 40) (40.2 ± 13.1 *vs.* 34.2 ± 10.3 ng/mL, $p < 0.05$). CART analysis identified plasma 4β-hydroxycholesterol concentration of 40.0 ng/mL as the cutoff value for discriminating between recipients with *CYP3A5*1* allele and those without this allele. According to our definition, recipients with *CYP3A5*1* allele (*CYP3A5*1/*1* or *CYP3A5*1/*3*) who had plasma 4β-hydroxycholesterol concentrations below 40 ng/mL were considered to show phenoconversion of CYP3A.

Table 2 shows the clinical data of 23 recipients with *CYP3A5*1* allele classified by the presence or absence of CYP3A phenoconversion. Phenoconversion of CYP3A was observed in 10 recipients with *CYP3A5*1* allele. No significant differences in eGFR, ALT and total bilirubin were observed between recipients with and those without CYP3A phenoconversion, suggesting that renal and hepatic functions were similar in the two groups. Similarly, no significant difference in total cholesterol was observed between two groups. Furthermore, no significant differences in all clinical data except for sex was observed between two groups.

3Plasma concentrations of indoxyl sulfate, intact-PTH, IL-6 and TNF-α in recipients with and those without CYP3A phenoconversion were compared (Fig. 1). Plasma indoxyl sulfate concentration was significantly higher in recipients with CYP3A phenoconversion compared to those without phenoconversion ($p < 0.05$, 95% CI of difference 1.33–20.6). On the other hand, plasma concentrations of intact-PTH, IL-6 and TNF-α were not significantly different between the two groups. In addition, plasma concentrations of indoxyl sulfate, intact-PTH, IL-6 and TNF-α did not differ between recipients with *CYP3A5*1* allele and those without *CYP3A5*1* allele (Fig. 2). Furthermore, plasma concentrations of 4β-hydroxycholesterol, indoxyl sulfate, intact-PTH, IL-6 and TNF-α did not correlate significantly with eGFR or elapsed time after transplantation (data not shown).

Discussion

In this study, phenoconversion of CYP3A, defined as a genotypic extensive/intermediate metabolizer (with *CYP3A5*1* allele) exhibiting CYP3A activity below the cutoff value that discriminates between extensive/intermediate and poor metabolizers, was observed in stable kidney transplant recipients, and plasma indoxyl sulfate concentration may have been involved in the phenomenon. This is the first report showing that accumulation of indoxyl sulfate may partially explain the gap in CYP3A activity unexplained by genetic contribution in patients with chronic renal failure, which is the greatest strength in this study.

The allele frequency of *CYP3A5*3* was 79.7% in our study, which agreed with previous studies in the Japanese population [27–29]. Plasma 4β-hydroxycholesterol concentration was significantly different between recipients with and those without *CYP3A5*1* allele as we reported previously [23,30]. 4β-hydroxycholesterol is formed by CYP3A4 and 3A5 [31,32] and is slowly eliminated from the circulation due to slow 7α-hydroxylation by CYP7A1 [33], which is not affected by renal failure [34]. These findings suggest that plasma 4β-hydroxycholesterol concentration is a suitable biomarker for CYP3A activity in patients with renal failure. Phenoconversion of CYP3A was found in 43.5% of the recipients with *CYP3A5*1* allele. To the best of our knowledge, this is the first report showing the occurrence of CYP3A phenoconversion in humans. In this study, we measured only *CYP3A5*3* as a genetic marker to judge the presence or absence of CYP3A phenoconversion, because *CYP3A5*3* is the major single nucleotide polymorphism in CYP3A [3] and a number of Japanese have *CYP3A5*3* allele [27–29]. There are other single nucleotide polymorphisms of CYP3A5 including *CYP3A5*2*, *CYP3A5*4*, and *CYP3A5*5*, as well as polymorphisms of CYP3A4 including *CYP3A4*1B*, *CYP3A4*4*, *CYP3A4*16*, *CYP3A4*18*, and *CYP3A4*22*. However, these polymorphisms are not frequent in the Japanese population [28,35–39]. Thus, they were not genotyped in this study.

The cutoff plasma 4β-hydroxycholesterol concentration for phenoconversion of CYP3A was set at 40.0 ng/mL in this study. This value was similar to the intermediate value between recipients with and without *CYP3A5*1* allele, which we reported previously [23,30]. We measured plasma concentrations of indoxyl sulfate, intact-PTH, IL-6 and TNF-α as candidate molecules involved in phenoconversion of CYP3A because they have been reported to cause downregulation of CYP3A in renal failure, and only plasma indoxyl sulfate concentration was significantly different between recipients with and those without CYP3A phenoconversion. Uremic toxins have been shown to alter CYP expression and function via transcriptional or translational modifications of CYP enzymes and direct inhibition of CYP-mediated metabolism [16–18]. Especially, indoxyl sulfate is implicated in decreased CYP3A activity in patients with chronic renal failure [23]. The detailed mechanism by which indoxyl sulfate downregulates CYP3A is unclear, but indoxyl sulfate is known to upregulate nuclear factor-κB (NF-κB) activity [40], and upregulation of NF-κB may decrease histone 4 acetylation in the CYP3A promoter [41], leading to downregulation of CYP3A expression. The detailed mechanisms by which PTH, IL-6, and TNF-α downregulate CYP3A are also unclear. PTH has been reported to downregulate CYP3A via activation of NF-κB, similar to indoxyl sulfate [19]. IL-6 and TNF-α may induce alteration of the subcellular location of retinoid X receptor-α [21,42], which heterodimerizes with the pregnane X receptor to regulate CYP3A expression [43]. Fifty-three of the 63 recipients (84.1%) in this study had renal failure as indicated by eGFR below 60 ml/min/1.73m^2, and their plasma indoxyl sulfate concentrations were above the normal range [44] with large inter-individual variability (12.0 ± 11.8 μM). On the other hand, plasma concentrations of intact-PTH, IL-6, and TNF-α were low in the recipients participating in this study, which could have contributed to the result of no association with CYP3A phenoconversion.

Table 2
Characteristics of kidney transplant recipients with *CYP3A5*1* allele classified by the presence or absence of CYP3A phenoconversion.

Characteristic	Phenoconversion	No phenoconversion	*p* value
No. of patients	10	13	NS
Males / females	10/0	6/7	$p < 0.01$
Age (year)	48.0 ± 9.9 [32-64]	51.6 ± 14.9 [26–74]	NS
Body weight (kg)	69.2 ± 14.3 [50.2-98.0]	55.9 ± 14.6 [43.4–81.2]	NS
White blood cell count (/μL)	6546 ± 2062 [3930-11600]	6845 ± 2674 [4050–13270]	NS
Total cholesterol (mg/dL)	182.9 ± 26.1 [139-226]	210.5 ± 33.5 [170–267]	NS
ALT (IU/L)	19.2 ± 8.7 [8.3-35.2]	14.5 ± 8.7 [6.1–38.6]	NS
Total bilirubin (mg/dL)	0.71 ± 0.19 [0.28-0.93]	0.59 ± 0.13 [0.38–0.80]	NS
eGFR (mL/min/1.73 m^2)	34.6 ± 17.4 [12.9-58.1]	46.1 ± 17.0 [18.6–78.5]	NS

ALT, alanine aminotransaminase; eGFR, estimated glomerular filtration rate. Data are expressed as number of subjects, or mean ± standard deviation [range].

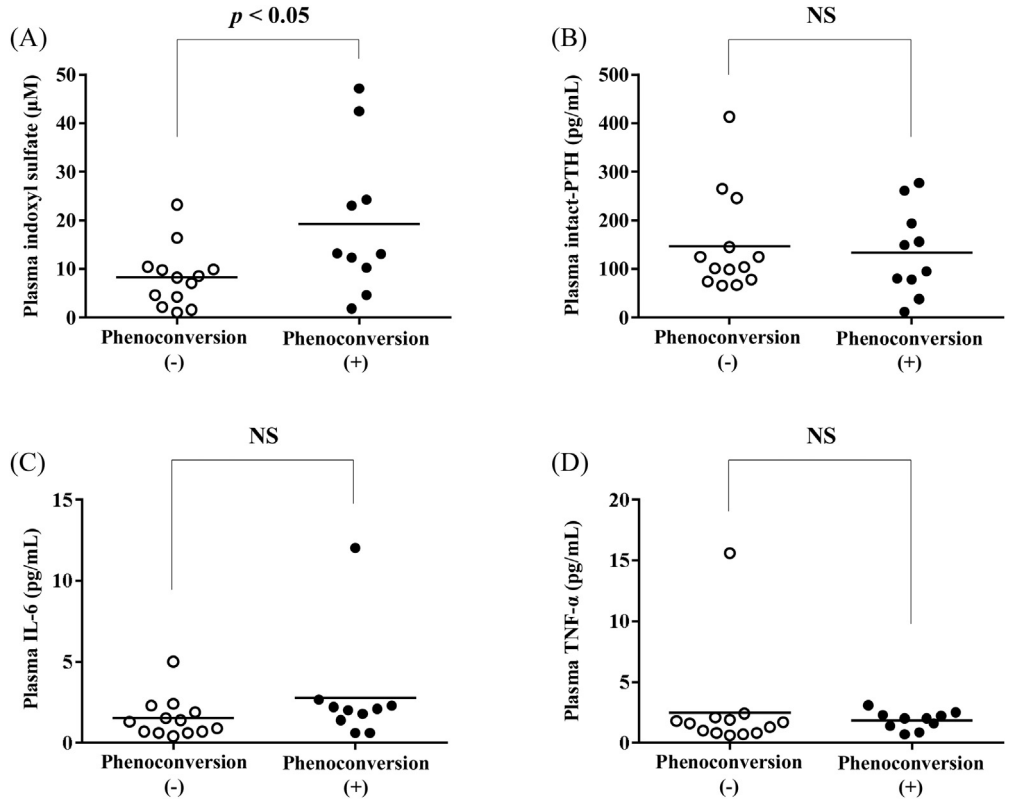

Fig. 1. Plasma concentrations of indoxyl sulfate (A), intact-PTH (B), IL-6 (C) and TNF-α (D) in stable kidney transplant recipients with and without phenoconversion of CYP3A.

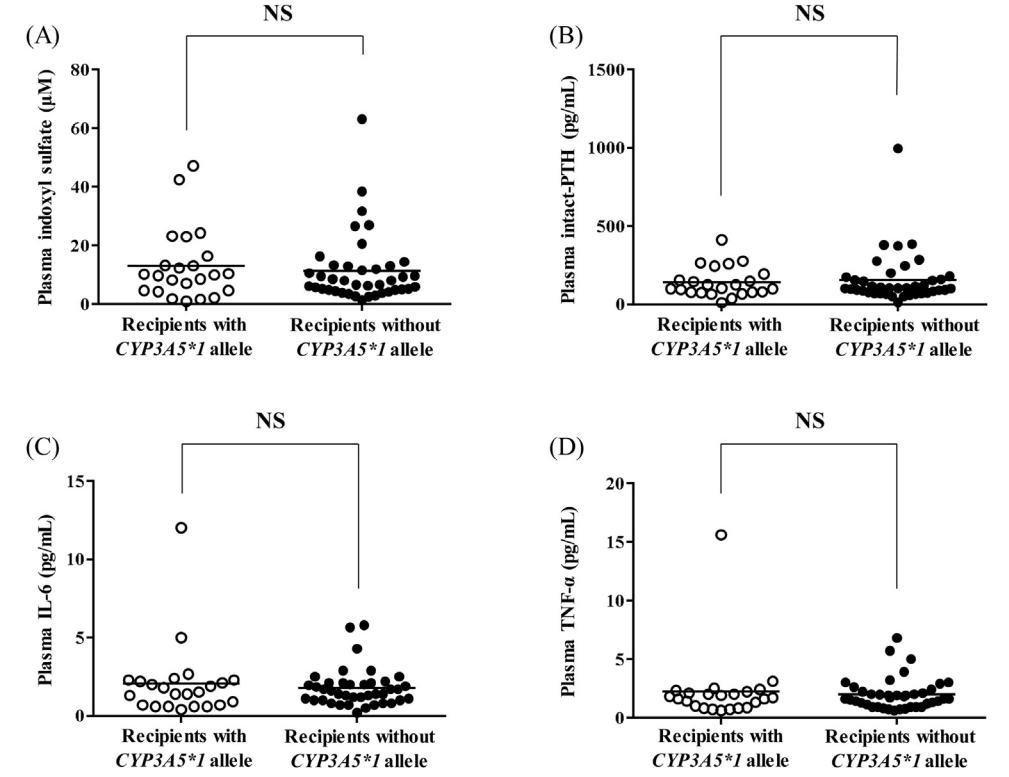

Fig. 2. Plasma concentrations of indoxyl sulfate (A), intact-PTH (B), IL-6 (C) and TNF-α (D) in stable kidney transplant recipients with and those without *CYP3A5*1* allele.

There is a limitation in this study. We demonstrated the relationship of CYP3A activity with plasma indoxyl sulfate concentrations in this study, but we were not able to evaluate the relationship between the pharmacokinetics of CYP3A substrate drugs and plasma indoxyl sulfate concentration. Further clinical study is needed to examine whether indoxyl sulfate is involved in the pharmacokinetics of CYP3A substrate drugs.

In conclusion, we demonstrated phenoconversion of CYP3A in stable kidney transplant recipients, and that higher plasma indoxyl sulfate concentrations in these subjects may be involved in the phenomenon. The present findings suggest that dose adjustment of drugs metabolized by CYP3A may be needed in patients with *CYP3A5*1* allele and high plasma indoxyl sulfate levels.

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Conflicts of interest

The authors declare no conflicts of interest to disclose.

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