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Original Investigation

Effect of CKD and Dialysis Modality on Exposure to Drugs Cleared by Nonrenal Mechanisms

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Background: Patients with kidney disease frequently experience adverse effects from medication exposure, even when drugs are cleared by nonrenal pathways. Although many studies suggest that nonrenal drug clearance is decreased in chronic kidney disease (CKD), there remains a paucity of in vivo studies in patients with varying degrees of decreased kidney function and those comparing the impact of dialysis modality (eg, hemodialysis [HD] and peritoneal dialysis [PD]).

Study Design: We performed in vivo clinical pharmacokinetic studies of midazolam, a nonrenally cleared specific probe for CYP3A4, and fexofenadine, a nonspecific probe for hepatic and intestinal transporters.

Setting & Participants: Healthy controls (n = 8), patients with non–dialysis-dependent (NDD)-CKD (n = 8), and patients receiving HD (n = 10) or PD (n = 8).

Outcomes: Exposure to midazolam and fexofenadine were quantified using area under the curve (AUC). Comprehensive pharmacokinetic parameters also were calculated for both probes.

Results: Midazolam AUC was significantly higher in the HD group (382.8 h·ng/mL) than in the healthy-control (63.0 h·ng/mL; $P < 0.001$), NDD-CKD (84.5 h·ng/mL; $P = 0.002$), and PD (47.4 h·ng/mL; $P < 0.001$) groups. Fexofenadine AUC was significantly higher in each of the NDD-CKD (2,950 h·ng/mL; $P = 0.003$), HD (2,327 h·ng/mL; $P = 0.01$), and PD (2,095 h·ng/mL; $P = 0.04$) groups compared with healthy controls (1,008 h·ng/mL).

Limitations: Small study groups had different proportions of diabetic patients, early stages of CKD not available.

Conclusions: Our data suggest that selection of dialysis modality is a major determinant of exposure to the CYP3A4 probe midazolam. Exposure to the intestinal and hepatic transporter probe fexofenadine is altered in patients with NDD-CKD and PD and HD patients. Thus, drug development and licensing of nonrenally cleared drugs should include evaluation in these 3 patient groups, with these results included in approved product information labeling. This reinforces the critical need for more in vivo studies of humans that evaluate the exposure to drugs cleared by these pathways.

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INDEX WORDS: Nonrenal drug clearance; drug metabolism; pharmacokinetics; cytochrome P450; CYP3A4; hepatic and intestinal drug transporters; hemodialysis (HD); peritoneal dialysis (PD); chronic kidney disease (CKD); adverse effects; medication exposure.

Patients with end-stage renal disease (ESRD) are prescribed an average of 8 to 12 medications,[1] with a significant median pill burden of 10 to 19 daily.[2] Significant morbidity is experienced due to medication accumulation and exposure in kidney disease, commonly leading to adverse events,[3] even when drug clearance is mediated by nonrenal mechanisms.[4] Current evidence suggests that nonrenal drug clearance may be affected in severe chronic kidney disease (CKD),[5-8] including persons with ESRD receiving hemodialysis (HD).[9-11]

Pathways responsible for nonrenal drug clearance include cytochrome P450 (CYP) enzymes and hepatic and intestinal drug transporters, including P-glycoprotein, organic anion-transporting polypeptides, and multidrug-resistance–associated protein transporters. A combination of these pathways likely is affected in both non–dialysis-dependent CKD (NDD-CKD) and patients receiving HD,[12] but the contribution of each component is uncertain.

CYP3A4 is the most abundantly expressed hepatic isozyme, representing ~35% of the total human liver

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CYP content and accounting for the metabolism of ~30% of all clinically used drugs.[13] Substantial evidence from studies of animals[5,14] and humans[15,16] supports decreased CYP3A-mediated metabolism of drugs in kidney disease. Emerging evidence also implicates impaired intestinal and hepatic transporter function in mediating altered pharmacokinetics in CKD.[6,7,12,15,17] However, most studies have focused on HD patients; less is known about their relative effects or the effect of peritoneal dialysis (PD) or NDD-CKD on drug exposure. Moreover, there is a paucity of in vivo human studies evaluating the exposure to nonrenally cleared drugs in patients with varying degrees of decreased kidney function, including those with NDD-CKD and those receiving HD or PD.

We hypothesized that severity of kidney disease and choice of dialysis modality differentially affect exposure to nonrenally cleared drugs. Using midazolam, a specific pharmacologic probe of CYP3A metabolism,[18] and fexofenadine, a nonspecific pharmacologic probe of intestinal and hepatic drug transporter activity,[19] we evaluated common pathways that may be important determinants of increased drug exposure in vivo in healthy individuals, patients with NDD-CKD, and patients receiving HD or PD.

METHODS

Study Participants

Participants were recruited from the CKD, HD, or PD clinics of the Southwestern Ontario Regional Renal Program. Participants with normal kidney function were recruited locally and primarily were employees of the London Health Sciences Center. All participants underwent a screening evaluation that included medical history, physical examination, and review of medications. Eligibility criteria included age 18 years or older, body mass index < 35 kg/m^2, and a negative pregnancy test if female and of childbearing age. Exclusion criteria included hepatic or gastrointestinal disease, prior solid-organ transplantation, prior adverse reaction to midazolam or fexofenadine, or medications known to interact with midazolam or fexofenadine.

Kidney function was evaluated with the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[20] In HD and PD patients, residual kidney function was calculated using interdialytic urinary collections.[21]

Patients avoided alcohol, grapefruit, or herbal supplements for 72 hours prior to the study. With consultation from their nephrologists, all routine medications were withheld on the study day. Known inducers or inhibitors of CYP3A4, P-glycoprotein, or organic anion-transporting polypeptides were withheld for 48 hours prior to the study day. Caffeine-containing products were prohibited on the study day, and patients fasted the morning of the study day.

Dialysis Modality and Study Day Timing

Hemodialysis

All HD patients underwent in-center intermittent conventional HD 3 times weekly for 3 to 4 hours per session for at least 3 months prior to study inclusion. HD adequacy is measured monthly as standard practice and exceeded NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) guidelines for average sessional single-pool dialysis adequacy (single-pool Kt/V) of 1.2 in all patients.[22] Pharmacokinetic data were collected in the Monday daytime of patients hemodialyzed Monday, Wednesday, and Friday evening or in the Tuesday daytime of patients hemodialyzed Tuesday, Thursday, and Saturday evening.

Peritoneal Dialysis

All PD patients had undergone daily nocturnal automated PD for at least 3 months prior to study inclusion. Dialysis adequacy is measured by standard practice every 3 months and exceeded NKF-KDOQI guidelines of total weekly Kt/V of 1.7 in all patients.[23] Pharmacokinetic data were collected after a complete overnight cycle, and patients were left day-dry after completion of the last cycle.

Study Design

Fasted patients had a 12-gauge intravenous catheter placed in an upper-limb peripheral vein and kept in situ for blood collection purposes. Patients were administered the CYP3A4 probe midazolam (1 mg diluted in 10 mL of saline solution, intravenous bolus over 1 minute) and the hepatic and intestinal drug transporter probe fexofenadine (120 mg orally) by a study physician at time zero (~8:00 AM). The catheter was flushed immediately with an additional 10 mL of saline solution. Blood samples were obtained immediately prior to time zero, then at 30, 60, 90, 120, 180, 240, 300, 360, and 480 minutes. All drug administration and blood collection were performed at the Centre for Clinical Investigation and Therapeutics in the Lindros Legacy Research Building at University Hospital, London, Canada.

Whole blood was centrifuged within 30 minutes of collection, and plasma was stored frozen at −80°C until analytical analysis. Additional blood samples also were used to determine baseline biochemical parameters. All baseline biochemical blood tests were performed using standardized methods by the London Laboratory Services Group at London Health Sciences Center.

Quantitation of Medication Exposure

Exposure to CYP3A4 probe was quantified using the area under the curve (AUC) for midazolam and 1-hydroxymidazolam. Plasma concentrations of total midazolam and 1-hydroxymidazolam were determined by liquid chromatography tandem mass spectrometry following a slightly modified method.[24]

Exposure to the hepatic and intestinal transporter probe was quantified using the AUC for fexofenadine. Plasma total fexofenadine concentration was determined by liquid chromatography coupled to fluorescence detection. Details of analytical methods can be found in Item S1 (provided as online supplementary material).

The AUC and all other pharmacokinetic parameters for midazolam, 1-hydroxymidazolam, and fexofenadine were estimated using Phoenix WinNonlin, version 6, software (Pharsight Corp) using standard noncompartmental methods. Details of the pharmacokinetic analysis also can be found in Item S1. Standard formulas for AUC (formula 1) and systemic drug clearance (CL; formula 2) were used to elucidate mechanisms of these outcomes.

$$\text{Formula 1: } AUC = (D)/(CL)$$

$$\text{Formula 2: } CL = (CL_{kidney}) + (CL_{hepatic}) + (CL_{other})$$

where D is drug dose, CL_{kidney} is kidney clearance, $CL_{hepatic}$ is hepatic clearance, and CL_{other} is clearance by other routes.

Statistical Analysis

Continuous variables were compared using 1-way analysis of variance. Categorical variables were compared using Fisher exact test and Bonferroni correction to adjust for multiple comparisons

(n = 6 for 4 groups). Statistical differences in log-transformed pharmacokinetic variables were determined by analysis of variance with the Holm-Sidak multiple comparison test. The correlation of midazolam and fexofenadine clearance with estimated glomerular filtration rate (eGFR) was determined by Pearson correlation analysis. Data are presented as mean ± standard deviation unless otherwise noted. $P < 0.05$ was required for statistical significance.

Ethics

Local ethics approval was provided by the Western University Health Sciences Research Ethics Board and all participants provided written informed consent (approval no. 16432). This study was consistent with the Declaration of Helsinki regarding ethical principles for medical research involving humans.

RESULTS

Baseline Demographic and Clinical Factors

There were 8, 8, 10, and 8 patients in the control, NDD-CKD, HD, and PD groups, respectively. No statistically significant differences occurred between groups for age, sex, race, height, weight, or body mass index (Table 1). Diabetes prevalence ranged from 0% to 60% of group participants and was present in none of the control group and 6 of 10 HD patients.

As expected based on our recruitment strategy, eGFR was higher in controls (94.8 mL/min/1.73 m^2) than in the NDD-CKD (17.0 mL/min/1.73 m^2; $P < 0.001$), HD (0.0 mL/min/1.73 m^2; $P < 0.001$), and PD (4.7 mL/min/1.73 m^2; $P < 0.001$) groups and higher in the NDD-CKD than the HD ($P < 0.001$) and PD groups ($P = 0.007$; Table 1). Other baseline biochemical parameters are summarized in Table 1. All patients completed the study and no significant adverse events were observed. In patients with diabetes, all blood glucose measurements were 5 to 15 mmol/L (90-270 mg/dL).

Effect of Kidney Disease and Dialysis Modality

Exposure to Midazolam

Exposure to midazolam and its principal metabolite 1-hydroxymidazolam was determined following a 1-mg intravenous dose (Fig 1A and B). $AUC_{0\rightarrow\infty}$ of midazolam for the HD group (382.8 h·ng/mL) was significantly greater than for the control (63.0 h·ng/mL; $P < 0.001$), NDD-CKD (84.5 h·ng/mL; $P = 0.002$), and PD (47.4 h·ng/mL; $P < 0.001$) groups (Table 2). There were no significant differences between patient groups in $AUC_{0\rightarrow\infty}$ of 1-hydroxymidazolam (Fig 1B; Table 2). The metabolic ratio (1-hydroxymidazolam AUC to midazolam AUC) was significantly lower in the HD group (0.026) than in the control (0.098; $P = 0.003$), NDD-CKD (0.091; $P = 0.01$), and PD (0.170; $P = 0.01$) groups.

Total systemic clearance of midazolam was significantly lower in the HD group (99.6 mL/min) compared with the control (282.3 mL/min; $P < 0.001$), NDD-CKD (242.9 mL/min; $P < 0.001$), and PD (428.2 mL/min; $P < 0.001$) groups. The terminal phase volume of distribution also was significantly lower in the HD group (31.9 L) compared with the control (106.3 L; $P < 0.001$), NDD-CKD (85.4 L; $P = 0.002$), and PD (175.8 L; $P < 0.001$) groups.

Table 1. Baseline Demographic and Clinical Data

Feature	Control (n = 8)	NDD-CKD (n = 8)	HD (n = 10)	PD (n = 8)
Age (y)	50.3 ± 10.7	57.3 ± 17.8	64.1 ± 13.8	70.0 ± 14.9
Sex (M:F)	3:5	6:2	4:6	3:5
White race	100.0	87.5	80.0	87.5
Height (cm)	173.6 ± 9.8	172.8 ± 3.9	165.2 ± 12.2	163.1 ± 7.1
Weight (kg)	75.0 ± 14.7	82.5 ± 14.1	78.0 ± 15.0	73.7 ± 14.5
Body mass index (kg/m^2)	25.1 ± 2.8	25.2 ± 1.1	27.9 ± 4.0	28.3 ± 2.7
Diabetes	0.0	12.5	60.0	37.5
eGFR (mL/min/1.73 m^2)	94.8 ± 4.3	17.0 ± 4.0[a]	0.0 ± 0.0[a]	4.7 ± 2.1[a]
Blood tests				
Serum creatinine (μmol/L)	69.3 ± 10.8	497.9 ± 361.7[a]	680.5 ± 200.7[a]	683.6 ± 214.8[a]
Parathyroid hormone (pmol/L)	3.1 ± 1.0	28.7 ± 21.3	44.1 ± 60.5	38.5 ± 20.9
Hemoglobin (g/L)	136.5 ± 6.7	115.9 ± 20.8[a]	115.0 ± 10.5[a]	109.8 ± 11.3[a]
Hematocrit (%)	40.3 ± 2.3	33.9 ± 5.7[a]	34.8 ± 3.6[a]	32.9 ± 3.8[a]
Ferritin (ng/mL)	66.8 ± 53.4	232.4 ± 177.0	283.8 ± 222.4	213.7 ± 153.5
C-Reactive protein (mg/L)	1.0 ± 0.6	1.5 ± 0.8	8.5 ± 8.1	9.2 ± 14.7
Albumin (g/L)	42.3 ± 2.9	41.5 ± 2.1	39.7 ± 3.5	38.0 ± 2.2[a]
ALT (U/L)	17.3 ± 6.1	14.4 ± 4.9	14.7 ± 9.6	13.5 ± 6.3
AST (U/L)	22.1 ± 4.2	15.9 ± 4.5[a]	14.1 ± 5.5[a]	16.9 ± 5.8

Note: Values for categorical variables are given as percentages; values for continuous variables, as mean ± standard deviation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HD, hemodialysis; NDD-CKD, non–dialysis-dependent chronic kidney disease; PD, peritoneal dialysis.

[a] $P < 0.05$ versus control.

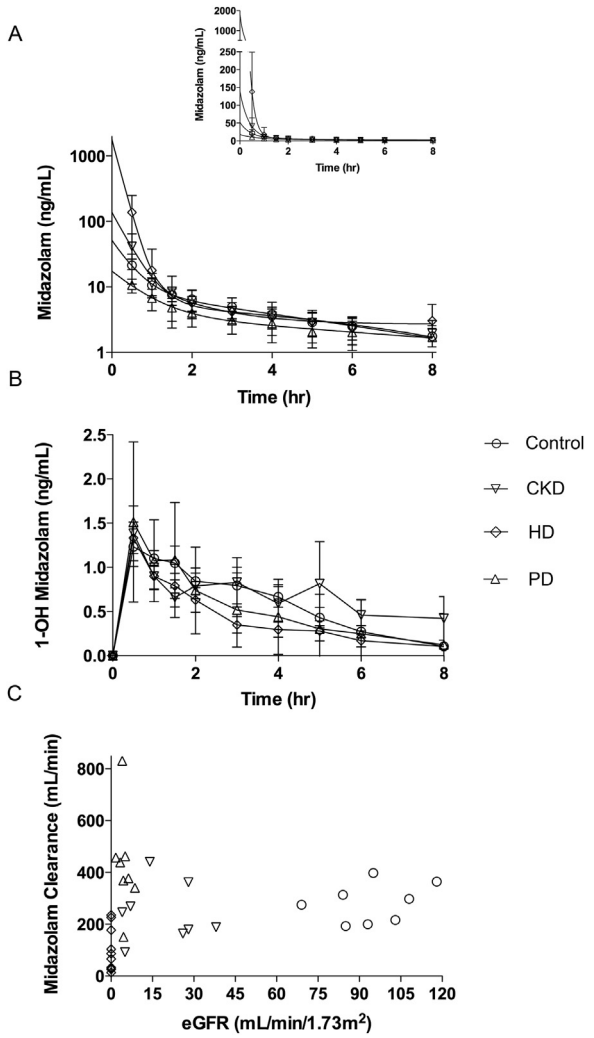

Figure 1. (A) Midazolam and (B) 1-hydroxymidazolam pharmacokinetics in healthy controls with normal kidney function (n = 8), patients with non–dialysis-dependent chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m^2 (n = 8), hemodialysis (HD) patients (n = 10), and nocturnal automatic peritoneal dialysis (PD) patients following a single intravenous dose of 1 mg of midazolam. Midazolam pharmacokinetics is shown on a log-linear scale with linear data shown inset. (C) Midazolam clearance is not correlated to eGFR ($r = 0.13$; $P = 0.5$). Data are mean ± standard deviation.

There were no differences in midazolam elimination half-life between groups. There were no significant differences between groups in peak concentration (C_{max}), AUC, or peak concentration time (T_{max}) of 1-hydroxymidazolam (Fig 1B, Table 2). Midazolam clearance was not correlated significantly with level of kidney function (Fig 1C).

Exposure to Fexofenadine

Exposure to fexofenadine was determined following a 120-mg oral dose (Fig 2). The fexofenadine $AUC_{0\rightarrow 8}$ was significantly higher in the NDD-CKD (2,950 h·ng/mL; $P = 0.003$), HD (2,327 h·ng/mL; $P = 0.01$), and PD (2,095 h·ng/mL; $P = 0.04$) groups compared with healthy controls (1,008.0 h·ng/mL; Fig 2; Table 3).

Fexofenadine clearance corrected for bioavailability ($CL/F_{0\rightarrow 8}$) was significantly lower in the NDD-CKD (52.7 mL/min; $P = 0.003$), HD (60.0 mL/min; $P = 0.01$), and PD (69.2 mL/min; $P = 0.04$) groups compared with healthy controls (135.0 mL/min). Similarly, the C_{max} of fexofenadine was significantly higher in the NDD-CKD (591.0 ng/mL; $P = 0.01$) and HD (531.1 ng/mL; $P = 0.03$) groups than in healthy controls (246.7 ng/mL). Fexofenadine clearance was correlated with kidney function as measured by eGFR ($r = 0.69$, $P < 0.001$; Fig 2B).

DISCUSSION

Patients with CKD, including ESRD, are especially susceptible to adverse effects from prescribed medications,[3] even when drug clearance is mediated by nonrenal mechanisms.[4] Risk is accentuated further by a high pill burden.[2] Clarifying appropriate medication doses in patients with kidney disease thus is critical not only in alleviating the risk of adverse events, but also to ensure clinical efficacy.[11]

A previous study by Nolin et al[17] investigated oral midazolam in HD patients, showing no differences in midazolam exposure compared with controls. These results were unexpected given the abundance of evidence implicating CKD with decreased CYP3A4-mediated metabolism.[17] In our study evaluating intravenous midazolam, HD patients had a 6-fold higher midazolam exposure (ie, AUC) than healthy controls (Table 2). The administration route may explain the differences between these studies. Orally administered midazolam is known to undergo extensive CYP3A4-mediated metabolism in the enterocyte, possibly masking the effect of altered hepatic clearance observed in our study.[25] Importantly, midazolam used clinically to sedate dialysis patients during procedures such as colonoscopy is administered intravenously; therefore, the large increase in exposure we observed may impart adverse medication events in HD patients.

An increased AUC typically occurs as a result of either an increase in the dose of the drug or a decrease in the drug's systemic clearance (formula 1). In our study, the midazolam dose (1 mg) was the same in all patients, indicating that decreased clearance mediates the increased drug exposure. Systemic clearance measured in this study is the sum of kidney clearance (CL_{kidney}), hepatic clearance ($CL_{hepatic}$), and a minor contribution of other clearance pathways (CL_{other}; formula 2). It is well appreciated that midazolam undergoes extensive hepatic clearance with negligible kidney excretion of unmetabolized drug.[26,27] In addition, our HD patients were anuric, ensuring that

Table 2. Medication Exposure Pharmacokinetic Estimates for Midazolam and 1-Hydroxymidazolam

Parameter	Control (n = 8)	NDD-CKD (n = 8)	HD (n = 10)	PD (n = 8)
Midazolam				
AUC $_{0\rightarrow\infty}$ (h·ng/mL)	63.0 ± 17.1	84.5 ± 44.6[a]	382.8 ± 368.8[b]	47.4 ± 26.8[a]
CL (mL/min)	282.3 ± 76.0	242.9 ± 113.3[a]	99.6 ± 84.6[b]	428.2 ± 190.6[a]
C_{max} (ng/mL)	51.8 ± 50.4	138.4 ± 181.9[a]	1,802 ± 2,348[b]	17.4 ± 4.8[a,c]
$V_{initial}$ (L)	35.3 ± 24.0	16.5 ± 12.7[a]	4.0 ± 5.2[b]	61.9 ± 19.1[a,c]
V_z (L)	106.3 ± 60.0	85.4 ± 33.4[a]	31.9 ± 29.9[b]	175.8 ± 58.1[a]
$t_{1/2}$ (h)	4.3 ± 2.2	4.2 ± 0.9	3.3 ± 0.7	5.6 ± 3.4
1-OH midazolam				
AUC $_{0\rightarrow\infty}$ (h·ng/mL)	5.7 ± 2.1	6.3 ± 3.9	4.2 ± 2.5	6.6 ± 7.0
C_{max} (ng/mL)	1.6 ± 0.5	1.9 ± 1.4	1.4 ± 0.5	1.5 ± 0.9
T_{max} (h)	1.3 (0.5-3.0)	0.8 (0.5-5.0)	0.5 (0.5-2.0)	0.5 (0.5-1.5)
Metabolic ratio[d]	0.098 ± 0.05	0.091 ± 0.09[a]	0.026 ± 0.03[b]	0.170 ± 0.17[a]

Note: Data are presented as mean ± standard deviation, except T_{max}, which is presented as median (range).

Abbreviations: AUC, area under the curve; CL, clearance; C_{max}, peak concentration; HD, hemodialysis; NDD-CKD, non–dialysis-dependent chronic kidney disease; PD, peritoneal dialysis; $t_{1/2}$, elimination half-life; T_{max}, time of peak concentration; $V_{initial}$, initial volume; V_z, volume of distribution.

[a] $P < 0.05$ versus HD.

[b] $P < 0.05$ versus control.

[c] $P < 0.05$ versus NDD-CKD.

[d] Ratio of 1-hydroxymidazolam AUC to midazolam AUC.

any minimal contribution of kidney clearance to midazolam disposition did not contribute to our findings. Accordingly, our data suggest that the 6-fold increase in midazolam exposure in HD patients is secondary to a decrease in hepatic clearance. It also must be noted that there are similar findings between our current study and that of Nolin et al[17]; both studies demonstrate that the terminal elimination half-life of midazolam and the AUC of midazolam's principal metabolite (1-hydroxymidazolam) did not differ between patient groups.

In addition to the decrease in clearance and increased AUC, we also observed a decrease in volume of distribution in HD patients compared with controls. The volume of distribution of a number of drugs is known to change in patients with kidney disease.[28] In our study, the volume of distribution of midazolam in the HD group was decreased significantly compared to that in both the control and PD groups. One possible explanation for the decrease in volume of distribution is that tissue binding of midazolam is altered in HD patients.[29] This also has been observed for other drugs, including digoxin, pindolol, and ethambutol.[29,30] Patients receiving daily nocturnal automated PD would be expected to have better acid-base homeostasis than the conventional HD patients in our study who were evaluated just before their next dialysis session. Accordingly, changes in the ionization of midazolam may occur in HD patients that promote trapping of midazolam within the intravascular compartment.

Midazolam total systemic clearance and the metabolic ratio of its principal metabolite[31] (1-hydroxymidazolam AUC to midazolam AUC) have long been considered the gold standard in vivo probes to assess CYP3A4-mediated metabolism in a wide spectrum of clinical settings.[17,24,31-33] In our study, we found that HD patients have decreased midazolam clearance and a decrease in metabolic ratio. Interestingly, the half-life of midazolam elimination was unchanged in the HD group compared to controls. In settings of CYP3A4 inhibition by drugs, midazolam half-life typically is increased, and similarly, when CYP3A4 is induced, midazolam half-life is decreased.[34,35] Our data demonstrating decreased midazolam clearance and metabolic ratio without a change in half-life highlight the complexity of pharmacokinetic changes in patients with kidney disease.

Kidney function also was a significant determinant of exposure to the nonrenally cleared intestinal and hepatic transporter substrate fexofenadine. AUC was increased significantly in each of the NDD-CKD (eGFR < 40 mL/min/1.73 m^2), PD, and HD groups compared to the healthy control group (Table 3). This was mediated by a decrease in systemic fexofenadine clearance. These data are consistent with a previous study evaluating fexofenadine pharmacokinetics in HD patients.[17] However, in our study, we show that patients with NDD-CKD (mean eGFR, 17.0 mL/min/1.73 m^2; Table 1) and PD patients also had increased fexofenadine exposure in vivo; this has not been described previously. A recent study by Joy et al[36] also confirmed a significant reduction in fexofenadine transporter activity in vivo in patients with CKD caused specifically by glomerulonephritis. Collectively, these data suggest that patients with

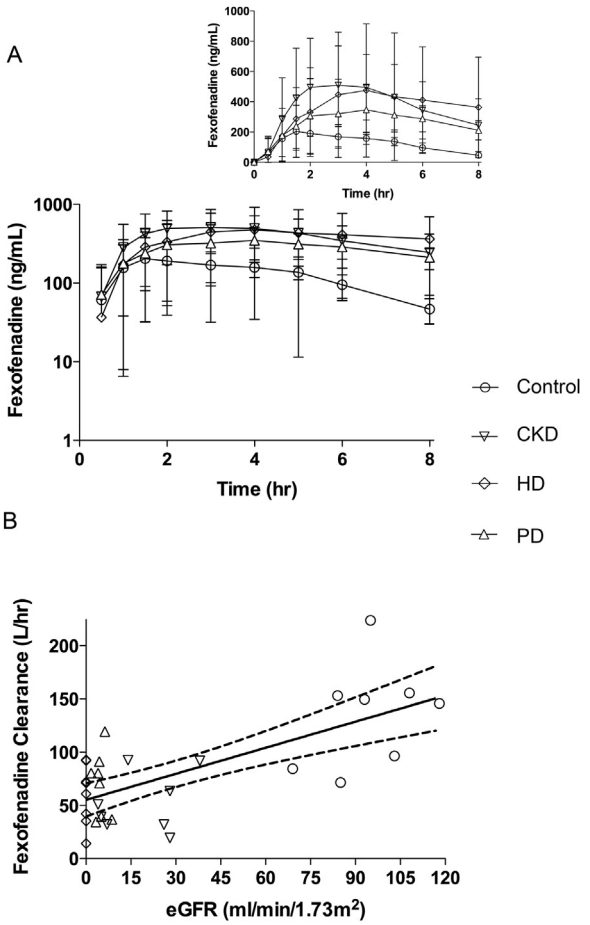

Figure 2. (A) Fexofenadine pharmacokinetics in healthy controls with normal kidney function (n = 8), patients with non–dialysis-dependent chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m^2 (n = 8), hemodialysis (HD) patients (n = 8), and nocturnal automatic peritoneal dialysis (PD) patients (n = 8) following a single oral dose of 120 mg. Data are shown on a log-linear scale with linear data shown inset and are mean ± standard deviation. (B) Fexofenadine clearance is correlated with kidney function (eGFR; $r = 0.7$; $P < 0.0001$, $y = 0.8x + 55.2$). Dotted lines represent 95% confidence intervals.

moderate to severe CKD have a reduction in nonrenal drug clearance pathways of transporter substrates similar to patients with ESRD requiring dialysis. This effect likely is mediated through altered expression and/or activity of P-glycoprotein and organic anion-transporting polypeptides. Unlike midazolam, fexofenadine clearance was correlated with eGFR, indicating that as kidney function declines, nonrenal clearance of the intestinal and hepatic transporter probe fexofenadine also decreases.

Possibly the most important observation in our study was the finding that exposure to the CYP3A4 probe intravenous midazolam, but not to the intestinal and hepatic transporter probe oral fexofenadine, is affected by dialysis modality. Several physiologic explanations may account for this. First, PD patients have a relatively consistent uremic environment, in contrast to the highly variable "peak and valley" uremic toxin concentrations found in HD patients.[37] Second, our PD patients were studied within 3 hours after completion of their most recent PD treatment, whereas HD patients were studied approximately 58 hours after their last HD session. Thus, severity of uremia, acid-base homeostasis, and volume overload differed substantially between the HD and PD groups.

Dialysis prescription affects the type and proportion of uremic toxins retained; thus, it is plausible that longer or more frequent PD or HD (eg, nocturnal daily HD) sufficiently alters the uremic milieu, reducing exposure to patients of factors that differentially inhibit the various pathways of nonrenal drug clearance (ie, CYP3A4 and drug transporters). All PD and HD patients in this study were receiving nocturnal intermittent PD and intermittent conventional HD, respectively, to prevent significant intragroup fluctuations in uremic toxins. However, small- and middle-molecule clearance differ in patients with longer or more frequent PD and HD. Therefore, while our study suggests that the specific type and proportion of uremic toxins may alter nonrenal drug clearance, 2 additional research questions need to be answered. First, the effect of dialysis type (PD vs HD), duration, and frequency must be determined. Second, metabolomic evaluation and characterization of the specific toxins, with identification of specific candidate toxins, should be completed. Only with further research in these 2 areas can more definitive conclusions be made.

Table 3. Medication Exposure Pharmacokinetic Estimates for Fexofenadine

Parameter	Control (n = 8)	NDD-CKD (n = 8)	HD (n = 8)	PD (n = 8)
$AUC_{0\rightarrow8}$ (h·ng/mL)	1,008 ± 393	2,950 ± 1,638[a]	2,327 ± 2,375[a]	2,095 ± 987[a]
$CL/F_{0\rightarrow8}$ (mL/min)	135.0 ± 49.3	52.7 ± 27.8[a]	60.0 ± 27.8[a]	69.2 ± 30.2[a]
C_{max} (ng/mL)	246.7 ± 135.2	591.0 ± 278.8[a]	531.1 ± 406.2[a]	413.9 ± 170.5
T_{max} (h)	1.8 (1.0-5.0)	2.5 (1.5-5.0)	4.0 (1.0-8.0)	4.0 (2.0-6.0)

Note: Data are presented as mean ± standard deviation, except T_{max}, which is presented as median (range).

Abbreviations: AUC, area under the curve; CL/F, clearance of fexofenadine; C_{max}, peak concentration; HD, hemodialysis; NDD-CKD, non–dialysis-dependent chronic kidney disease; PD, peritoneal dialysis. T_{max}, time of peak concentration.

[a] $P < 0.05$ versus control.

There are numerous published guidelines for drug dosing in patients with decreased kidney function,[38-43] but there continues to be inadequate evidence to properly dose many commonly used medications. For the 20 top sold medications in the United States,[44] there was either no recommendation regarding dosing or the need for dose adjustment was unknown in 5 (25%), 16 (80%), and 12 (60%) of the medications in NDD-CKD, PD, and HD, respectively (Table S1).[45] This lack of evidence also is pervasive in medications most prescribed to dialysis patients (Table S2), in which there was no recommendation regarding dosing or the need for dose adjustment was unknown for 40% of medications in each of PD and HD. Many of these medications are substrates for either CYP3A4 (50% and 60% in Tables S1 and S2, respectively) or intestinal and hepatic transporters (75% and 45% in Tables S1 and S2, respectively).[46] This reinforces the critical need for more in vivo studies of humans that evaluate the exposure to drugs metabolized by these pathways.

We must note that our study had some limitations, including that our study groups differed in prevalence of diabetes mellitus. Diabetes has been associated with decreased hepatic CYP3A4 enzyme activity and protein levels in ex vivo studies examining midazolam metabolism by human liver microsomes.[47] Likewise, experimental diabetes has been shown to decrease intestinal P-glycoprotein activity, altering AUC and C_{max} of orally administered taxanes in rats.[48] However, in the current study, fexofenadine exposure was increased significantly in the NDD-CKD group, in which only 1 of 8 patients had diabetes mellitus, and clearance correlated well with kidney function. Similarly, HD patients experienced a large increase in midazolam exposure, whereas PD patients did not. Although the results suggest that diabetes did not play a role, the disproportionate numbers of diabetic patients in the study groups complicate data interpretation. Future studies including a group of diabetic controls without CKD will be an important consideration. In addition, due to limitations with scheduling the HD patients, we were unable to continue the fexofenadine pharmacokinetic study beyond 8 hours and were forced to use a limited sampling approach that terminated at 8 hours. Although the terminal elimination rate and half-life of fexofenadine could be calculated accurately in healthy controls, we could not calculate this parameter accurately in the NDD-CKD, HD, or PD groups. This was due to the drastic change in exposure in these patients. Longer time to complete additional sampling would have been impractical due to the dialysis schedules of our patients. Nevertheless, our data convincingly demonstrate that NDD-CKD, HD, and PD significantly increased fexofenadine exposure. Importantly, our observed increases in fexofenadine $AUC_{0\rightarrow 8}$ in the NDD-CKD, HD, and PD groups of 2.9-, 2.3-, and 2.1-fold, respectively, were similar to the increase in $AUC_{0\rightarrow\infty}$ reported previously in HD patients (2.8-fold increase)[17] and patients with glomerulonephritis (2.0-fold increase).[36] It also is important to note that other studies have used limited sampling strategies to successfully characterize the pharmacokinetics of drugs.

Despite these limitations, this study also has notable strengths. Namely, patients with varying levels of kidney function (NDD-CKD and ESRD treated with 2 different dialysis modalities) were evaluated in vivo. We thus could make conclusions about the variable impact of uremia and the effect of dialysis modality on exposure to the CYP3A4 probe midazolam and the intestinal and hepatic transporter probe fexofenadine.

The US Food and Drug Administration, which has published an updated draft guidance document, has recognized the pharmacokinetics of drugs in patients with kidney disease as important in optimal and safe drug therapy.[16,49] Our study adds the important finding that exposure to intravenous midazolam is increased 6-fold in vivo in HD patients compared with healthy controls. Surprisingly, this difference was not observed in PD patients. The more than 8-fold increase in midazolam exposure in HD compared with PD patients clearly indicates that dialysis modality substantially influences dosing requirement for some drugs in the setting of kidney disease. We also demonstrate that exposure to the intestinal and hepatic transporter probe drug fexofenadine is increased in vivo, not only in HD and PD patients, but also in patients with NDD-CKD. This study confirms a physiologic basis for the increased exposure and therefore susceptibility to drug toxicity in patients with CKD, including those with ESRD treated with dialysis. Further research is required to optimize medication dose, minimize toxicity, and maximize clinical efficacy for nonrenally cleared medications in patients with either NDD-CKD or ESRD treated with HD or PD.

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SUPPLEMENTARY MATERIAL

Table S1: Top 20 sold oral medications in United States, 2013.

Table S2: Top 20 medications prescribed to Part D–enrolled dialysis patients, 2008.

Item S1: Details about analytical assays and pharmacokinetic analysis.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2014.09.015) is available at www.ajkd.org

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