

# Verification of *in vitro* system for predicting hemodialysis clearance of drugs

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## Purpose

Prediction of human PK profile is very important challenge for drug development. We have developed *in vitro* system for evaluating hemodialysis clearance, which is needed to predict PK profile in hemodialysis patients. To verify this *in vitro* system, hemodialysis clearance of pregabalin was predicted using this system and compared with clinical data.

## Materials

Pregabalin was used as a test article. The miniaturized dialyzers made of hollow fibers cut from the dialyzer, TORAYLIGHT® NV (Toray Medical), were used for *in vitro* study. TORAYLIGHT® NV were used for clinical study.

Miniaturized dialyzer	
Original dialyzer	TORAYLIGHT® NV
Material	Polysulfone
Length (cm)	10
Number of hollow fibers	42
Membrane area (cm <sup>2</sup> )	26.4

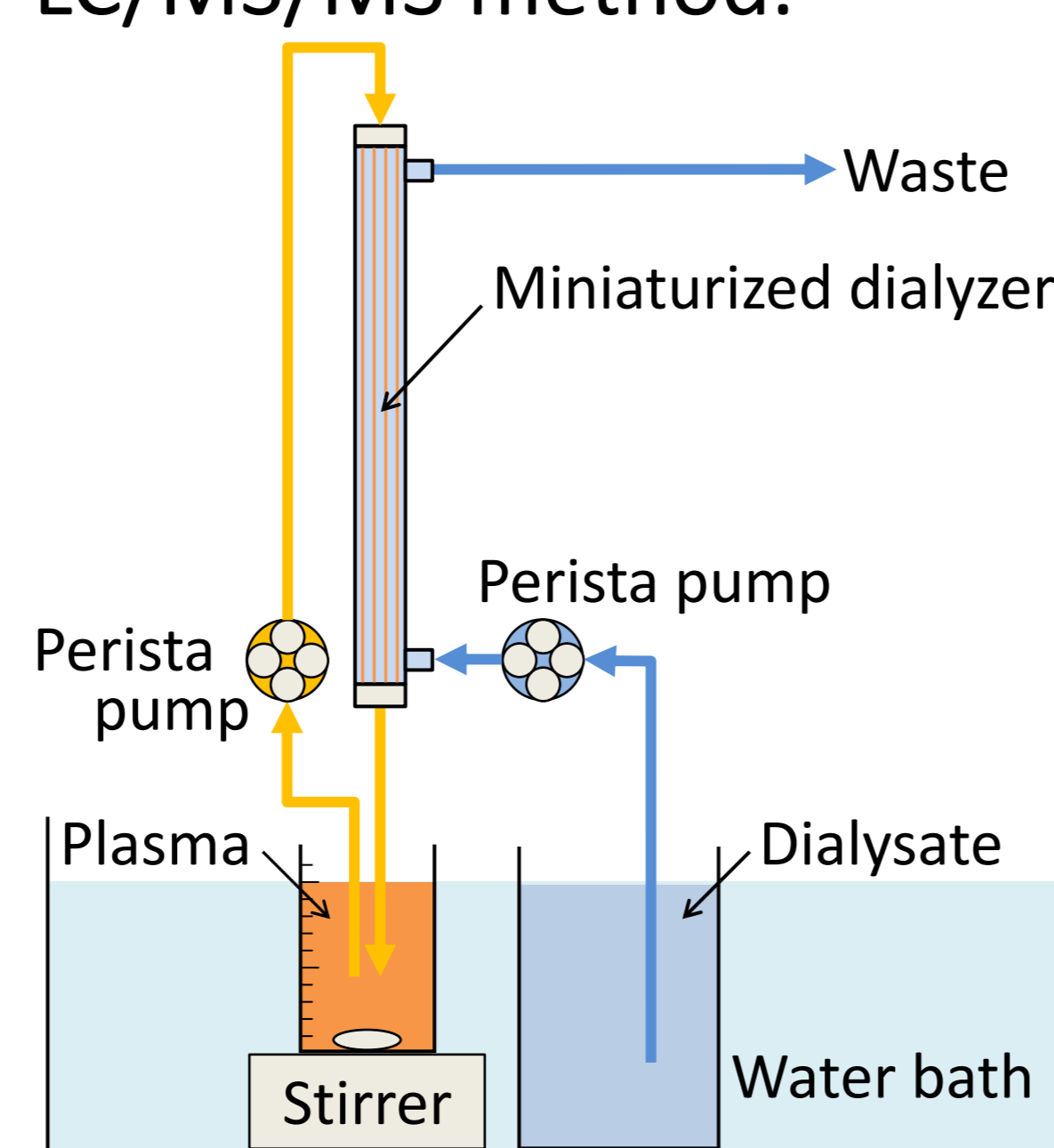


## Methods

### *In vitro* study

Human plasma containing pregabalin was dialyzed under the following conditions, and pregabalin concentrations in plasma at 0, 15, 30, 60, 90 and 120 min were measured by LC/MS/MS method.

Dialysis conditions	
Dialysate	Physiological saline
Test concentration	5000 ng/mL
Plasma volume	20 mL
Dialysis period	120 min
Temperature in water bath	37°C
Flow rate	
Plasma	1.6 to 2.2 mL/min
Dialysate	4.5 to 6.5 mL/min



### Clinical study

As for four hemodialysis patients with TORAYLIGHT® NV taking pregabalin, the pregabalin concentrations in plasma at inlet and outlet of hemodialyzer were measured to calculate hemodialysis clearance.

This study was conducted in accordance with ethical guidelines for clinical studies, and obtained written informed consent from all study subjects.

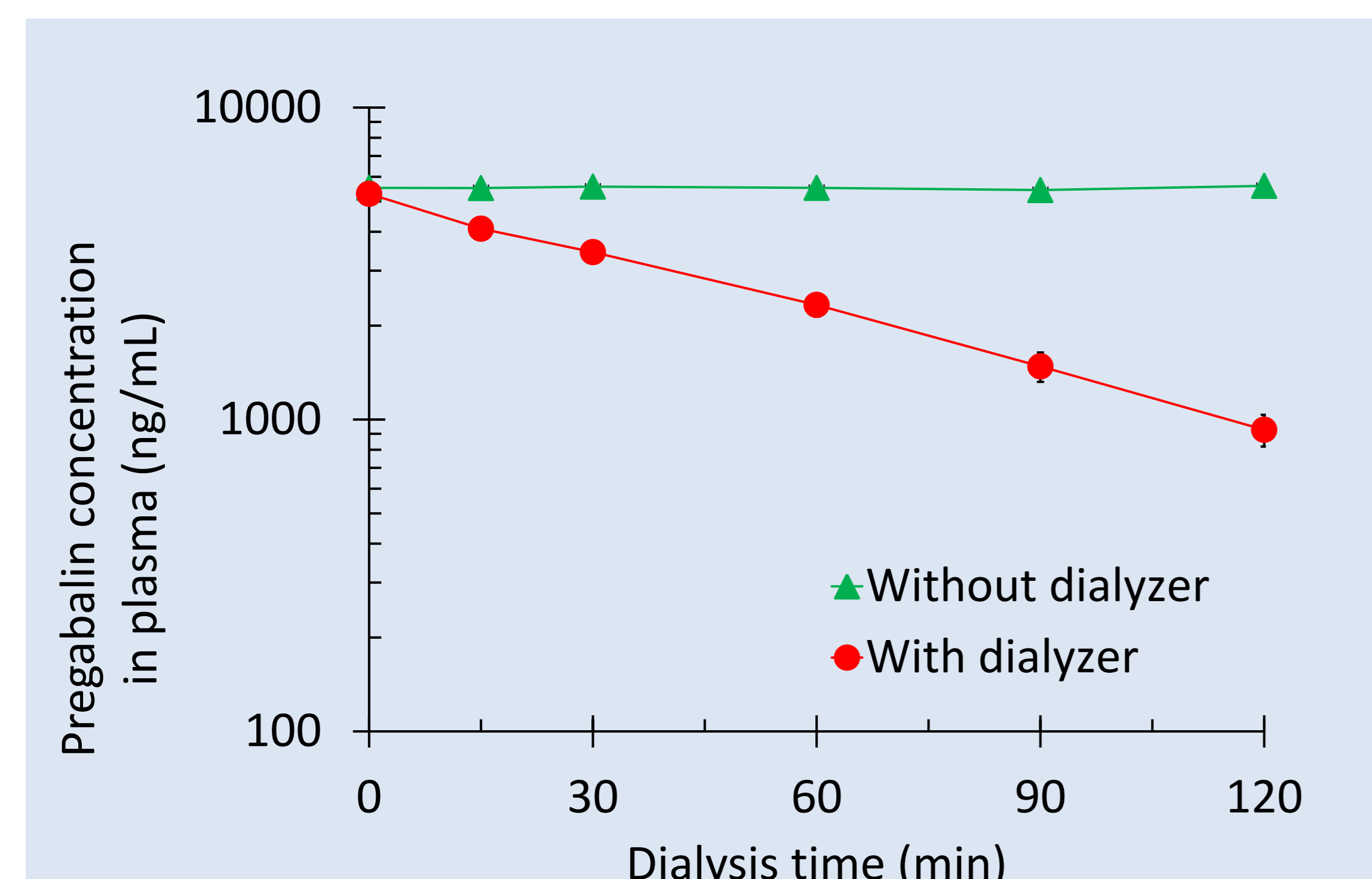
### Data analysis

Dialysis parameters	Formula
Elimination constant ( $k_{el}$ )	$C_t = C_0 \times \exp(-k_{el} \times t)$
<i>In vitro</i> dialysis clearance ( $CL_{D,vitro}$ )	$CL_{D,vitro} = k_{el} \times V$
Mass transfer coefficient (K)	$K = \frac{Q_{P,vitro}}{A_{vitro} \times (1 - Z_{vitro})} \times \ln \frac{1 - E_{vitro} \times Z_{vitro}}{1 - E_{vitro}}$
	$E_{vitro} = \frac{CL_{D,vitro}}{Q_{P,vitro}}, \quad Z_{vitro} = \frac{Q_{P,vitro}}{Q_{D,vitro}}$
Predicted clinical hemodialysis clearance ( $CL_{D,pred}$ )	$CL_{D,pred} = Q_P \times \frac{1 - \exp[K \times A/Q_P \times (1 - Q_P/Q_D)]}{Q_P/Q_D - \exp[K \times A/Q_P \times (1 - Q_P/Q_D)]}$
Observed clinical hemodialysis clearance ( $CL_{D,obs}$ )	$CL_{D,obs} = Q_P \times (C_{inlet} - C_{outlet})$

$A_{vitro}$ , membrane area of miniaturized dialyzer;  $C_0$ , concentration at 0 min;  $C_t$ , concentration at  $t$  min;  $C_{inlet}$ , concentration at inlet of hemodialyzer;  $C_{outlet}$ , concentration at outlet of hemodialyzer;  $Q_{P,vitro}$ , dialysate flow in *in vitro*;  $Q_{D,vitro}$ , plasma flow in *in vitro*;  $V$ , plasma volume (20 mL);  $A$ , membrane area of hemodialyzer;  $Q_P$ , plasma flow in clinical;  $Q_D$ , dialysate flow in clinical

## Results

### *In vitro* study



Human plasma containing pregabalin was circulated with miniaturized dialyzers and without a miniaturized dialyzer for 120 min. Data expressed as mean  $\pm$  SD (n=3).

Dialysis parameters of pregabalin in <i>in vitro</i> study	
K (1/min)	0.0143 $\pm$ 0.0009
$CL_{D,vitro}$ (mL/min)	0.285 $\pm$ 0.019
K (cm/min)	0.0121 $\pm$ 0.0009

Data expressed as mean  $\pm$  SD (n=3).

### Clinical study

Subjects (Hemodialysis patients)	Hemodialysis conditions			Hemodialysis clearance of pregabalin (based on plasma concentration)			
	No.	Hematocrit	Membrane area	Blood flow	Dialysate flow	Observed	Predicted*
	1	38.1%	1.6 m <sup>2</sup>	250 mL/min	500 mL/min	109 mL/min	103 mL/min
	2	36.0%	1.6 m <sup>2</sup>	180 mL/min	500 mL/min	74.6 mL/min	89.2 mL/min
	3	34.5%	1.6 m <sup>2</sup>	180 mL/min	500 mL/min	97.8 mL/min	90.4 mL/min
	4	30.5%	1.6 m <sup>2</sup>	200 mL/min	500 mL/min	114 mL/min	98.1 mL/min

\* Data were predicted from *in vitro* study, assuming that mass transfer coefficient (K) of clinically used hemodialyzer is consistent with that of miniaturized dialyzer

#### Information of pregabalin cited from the package insert

No binding to plasma protein,  $V_d/F=40$  L, B/P ratio=0.76,  $M_w=159.23$

Pregabalin concentrations in plasma of hemodialysis patients were decreased to approximately 50% after 4 hr hemodialysis, and hemodialysis clearance was 192 mL/min.

## Conclusions

Predicted hemodialysis clearance of pregabalin was consistent with clinical data. Therefore this *in vitro* system is a very useful and convenient tool for predicting hemodialysis clearance. Using PBPK model incorporating the predicted hemodialysis clearance, it is expected that PK profile in hemodialysis patients can be accurately simulated.