In Vitro Miniaturized Dialysis System, Useful Tool for Prediction of Drug Removal Efficiency in Hemodialysis

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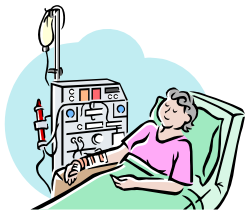
Purpose

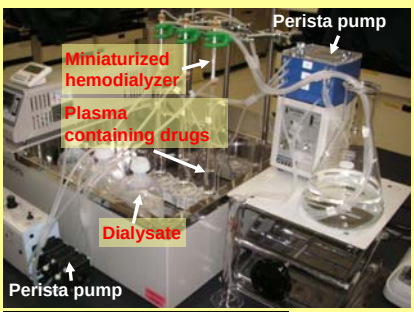


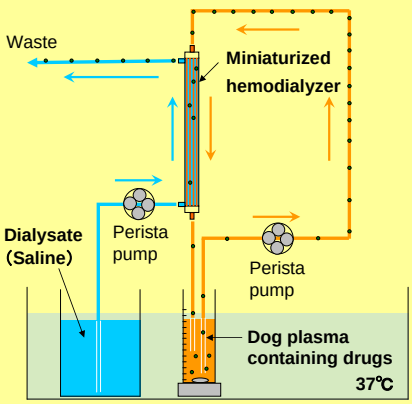
Quantitative evaluation of drug removal by hemodialysis is becoming more important in the drug development process as well as in clinical practice for hemodialysis patient. Furthermore, information of drug removal efficiency by hemodialysis gives useful judgment whether hemodialysis is an effective treatment for drug overdose patient or not. We have reported that *in vitro* miniaturized dialysis system using human plasma is a simple method to predict drug removal efficiency by hemodialysis. **The purpose of this study was to demonstrate the correlativity of drug removal efficiency obtained by hemodialysis in dogs (animal hemodialysis model) and that predicted by *in vitro* miniaturized dialysis system using dog plasma.**

Methods and Results

In Vitro Miniaturized Dialysis System

in vitro miniaturized dialysis system





Drugs: Vancomycin, Procainamide, Diclofenac, Propafenone (mixture)

Dialysis

Dialyzer: Miniaturized dialyzer of Toraysulfone*
* Polysulfone, Toray Medical, Inc.

Period: 120 min

Prediction of hemodialysis clearance of animal hemodialysis model

1. Calculate *in vitro* hemodialysis clearance (CL_{vitro})

$$C = C_0 \times \exp\left(-\frac{CL_{vitro}}{V} \times t\right)$$

C: Drug concentration in plasma at t min
C_0: Drug concentration in plasma at 0 min
t: Time after hemodialysis
V: Plasma volume

2. Calculate overall mass transfer coefficient (K)

$$K = \frac{Q_{P,vitro}}{A_{vitro} \times (1-Z)} \times Ln\left(\frac{1-E \times Z}{E}\right) \quad E = \frac{CL_{vitro}}{Q_{p,vitro}} \quad Z = \frac{Q_{p,vitro}}{Q_{D,vitro}}$$

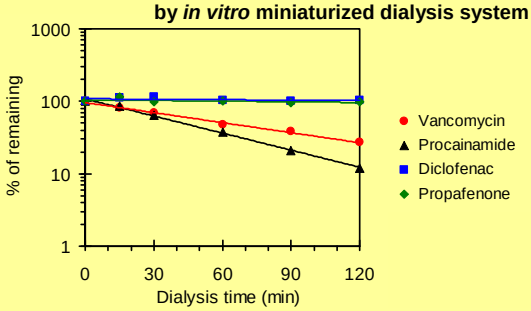
A_{vitro}: Effective membrane area of miniaturized hemodialyzer
$Q_{D,vitro}$: Dialysate flow rate of *in vitro* miniaturized dialysis system
$Q_{P,vitro}$: Plasma flow rate of *in vitro* miniaturized dialysis system

3. Predict hemodialysis clearance (CL_{pred}) of animal hemodialysis model

$$CL_{pred} = Q_{P,vivo} \times \frac{1-\exp[N_T \times (1-Z)]}{Z-\exp[N_T \times (1-Z)]} \quad N_T = \frac{K \times A_{vivo}}{Q_{P,vivo}} \quad Z = \frac{Q_{P,vivo}}{Q_{D,vivo}}$$

A_{vivo}: Effective membrane area of hemodialyzer used in animal hemodialysis model
Ht: Hematocrit
$Q_{B,vitro}$: Blood flow rate in animal hemodialysis model
$Q_{D,vitro}$: Dialysate flow rate in animal hemodialysis model
$Q_{P,vitro}$: Plasma flow rate of in animal hemodialysis model, $Q_p = (1 - Ht) \times Q_B$

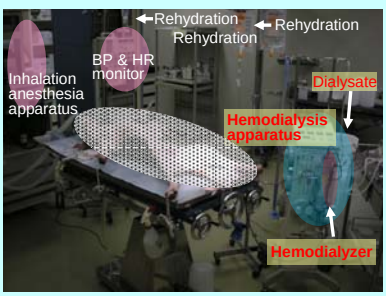
Drug concentration in plasma during dialysis by _in vitro_ miniaturized dialysis system



Drug removal parameter of in vitro miniaturized dialysis system and predicted hemodialysis clearance of animal hemodialysis model

Drugs	CL_{vitro} (mL/min)	K (cm/min)		CL_{pred} (mL/min)
Vancomycin	0.213	8.70×10^{-3}	Prediction →	**42.8**
Procainamide	0.361	1.57×10^{-2}	$Q_{B,vivo}$: 100 mL/min $Q_{D,vivo}$: 250 mL/min A_{vivo}: 1.0 m²	**52.3**
Diclofenac	Not dialyzed	-		-
Propafenone	Not dialyzed	-		-

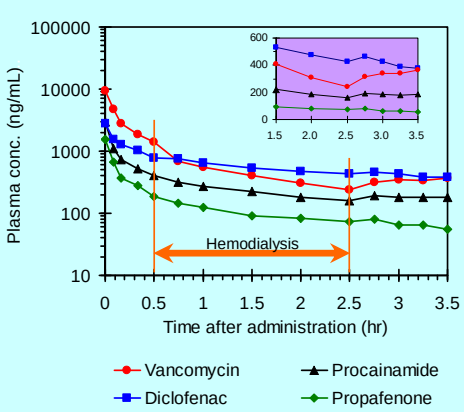
Animal Hemodialysis Model (Dog)



Drugs (Cassette, i.v.)
Vancomycin (0.25 mg/kg), Procainamide (0.1 mg/kg), Diclofenac (0.1 mg/kg), Propafenone (1 mg/kg)

Hemodialysis
Hemodialyzer: Toraysulfone, 1.0 m²
(Polysullfone, Toray medical, Inc.)
Flow rate: Blood; 100 mL/min
Dialysate; 250 mL/min
Period: 0.5 hr to 2.5 hr after administration

Plasma concentration profile in animal hemodialysis model



Hemodialysis clearance of animal hemodialysis model

Drugs	Concentration (ng/mL)		CL_{vivo}
	Inlet*	Outlet*	(mL/min)
Vancomycin	243	133	**44.3**
Procainamide	156	82	**46.6**
Diclofenac	452	456	Not dialyzed
Propafenone	74	77	Not dialyzed

* Inlet and outlet port of hemodialyzer

Conclusion

In vitro miniaturized dialysis system is a useful tool for prediction of drug removal efficiency in hemodialysis