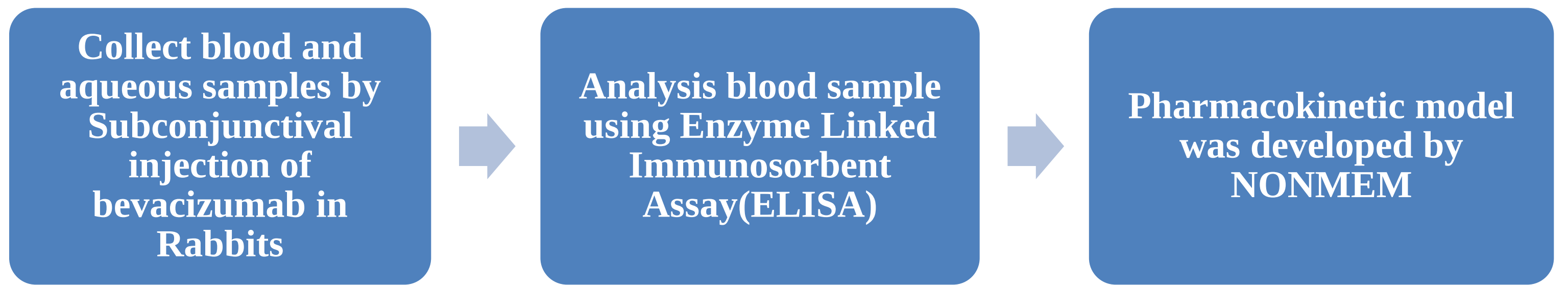


Introduction

Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A(VEGF-A). Recent studies have shown that intravitreal or intracameral injection of bevacizumab, a full length anti-VEGF antibody, may be a useful adjunct in the treatment of neovascular glaucoma. One way of delivering macromolecules is subconjunctival injection. But in each eye, the concentration of bevacizumab has different conditions. Pharmacokinetic model for subconjunctival administration of bevacizumab had not been developed yet. In this study, we developed pharmacokinetic model for subconjunctival administration of bevacizumab

Method

Scheme of the study



- New Zealand white rabbits were administrated at dose of 2.5mg of bevacizumab by subconjunctival injection route.
- Sampling time were 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 120, 168 hour after the injection.
- Bevacizumab concentrations were measured in aqueous fluid of injected and un-injected eyes and serum using enzyme-linked immunosorbent assay.
- Pharmacokinetic model was developed by NONMEM.

Study design

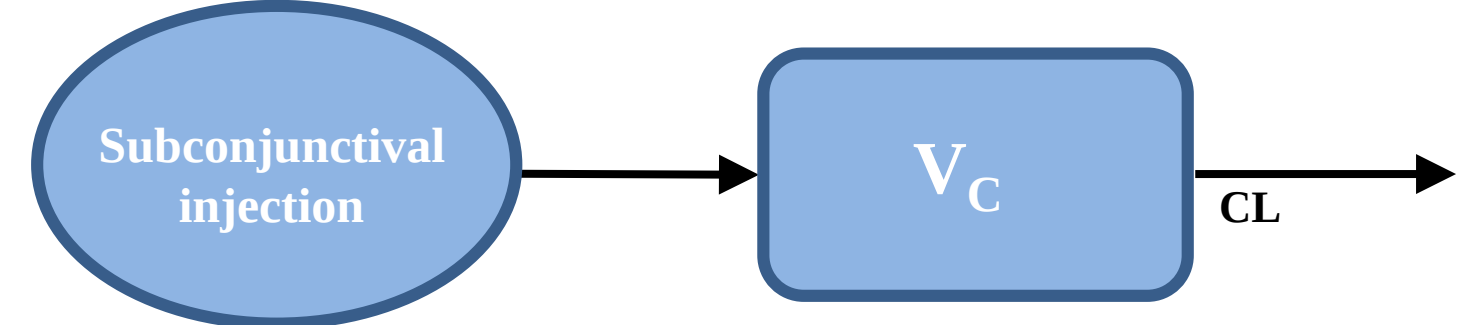
◆ Pre-Clinical test

- Animal type : New Zealand white rabbits, female, 2.5~3.0 kg
- Dosage : A single dose of 2.5 mg of bevacizumab subconjunctival injection.
- Sample type : Blood samples, Aqueous samples
- Sampling time : 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 120, 168 hour after the injection.
- Analysis method : Enzyme linked immunosorbent assay

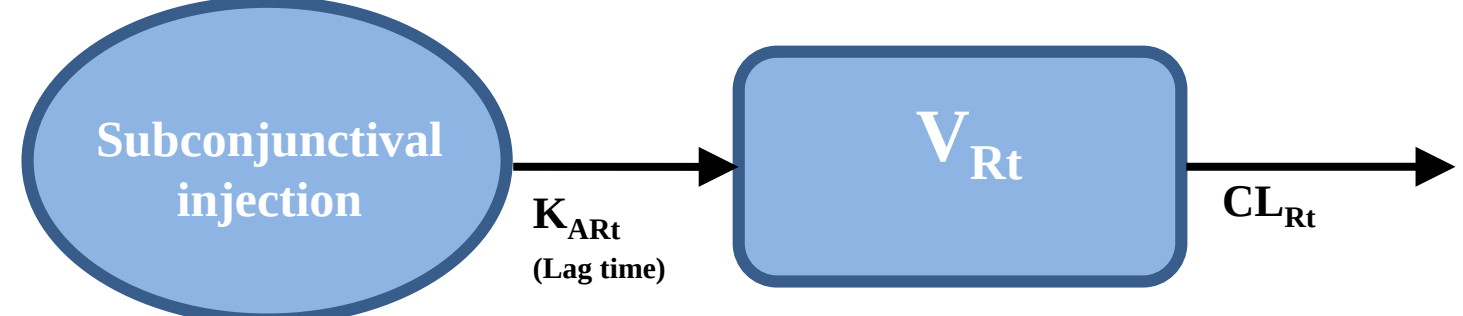
Pharmacokinetic modeling

◆ 1-STEP (separated compartments)

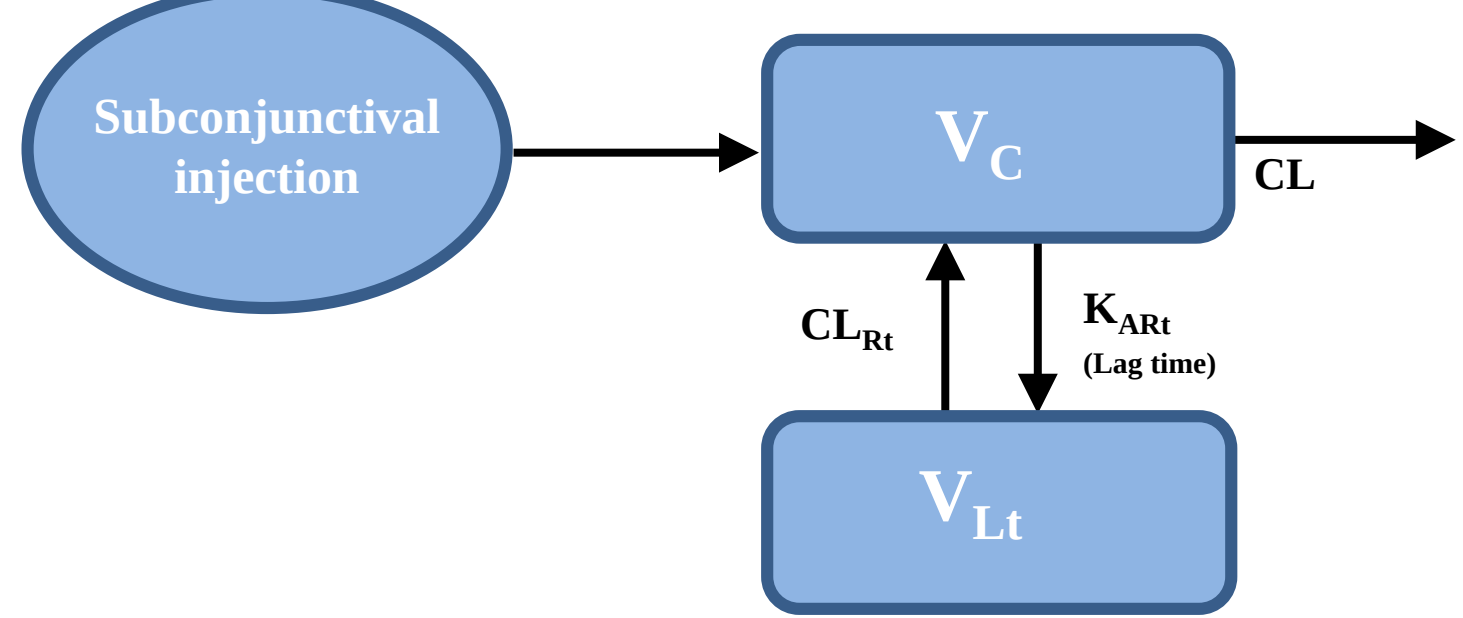
- Central compartment



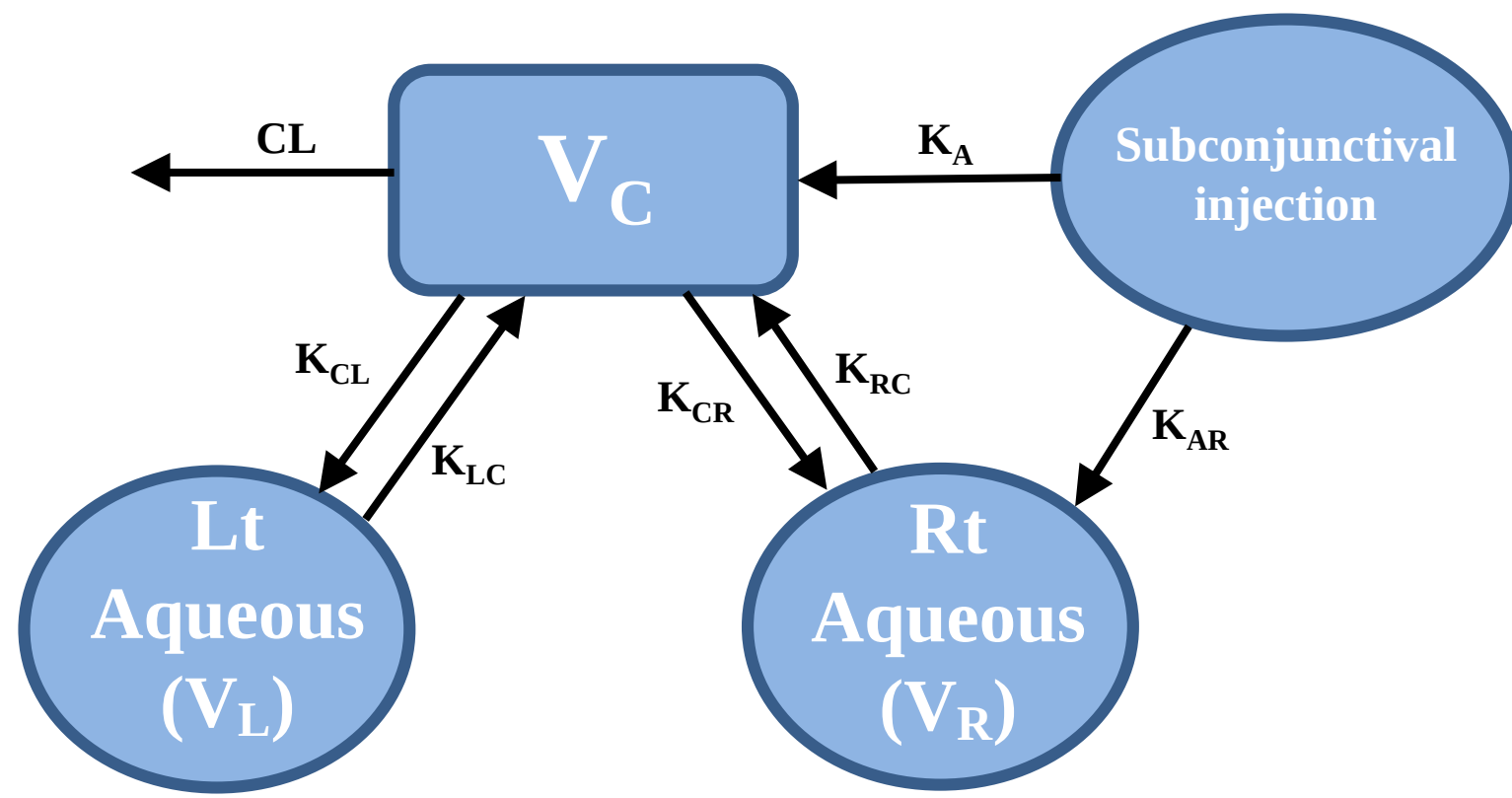
- Right Aqueous compartment



- Left Aqueous compartment



◆ 2-STEP (multi-complex compartments)



◆ Model evaluation

- Goodness of fit plot (GOF)
 - Conditional weighted residual versus time and observation versus individual prediction plots
- Visual predictive check(VPC) of the model (using the software PsN)
 - the 95% confidence interval of 5th,50th,95th percentile simulated concentration was obtained and graphically compared with the observed data

Results

Pharmacokinetic parameters from PK modeling

- As result of subconjunctival injection pharmacokinetic modeling, multi-complex compartments model is good prediction model.
- Injected side aqueous has higher concentration of bevacizumab than the other side aqueous
- Bevacizumab was measured at both side aqueous after 12hr injected drug

◆ 1-STEP(separated compartments)

Table1. pharmacokinetic parameter value of 1-step(separated compartment)

Parameter	Value		
	Central	Rt Aqueous	Lt Aqueous
OFV	117.207	67.542	36.846
Ka	-	0.561	0.0805
Volume	23.9	29.6	68.3
Clearance	0.299	0.694	1.76
Lag-time	-	11.9	11..3
Residual error			
Additive error	0(fixed)	0.892	0.868
Proportional error	0.142	0.315	0.245

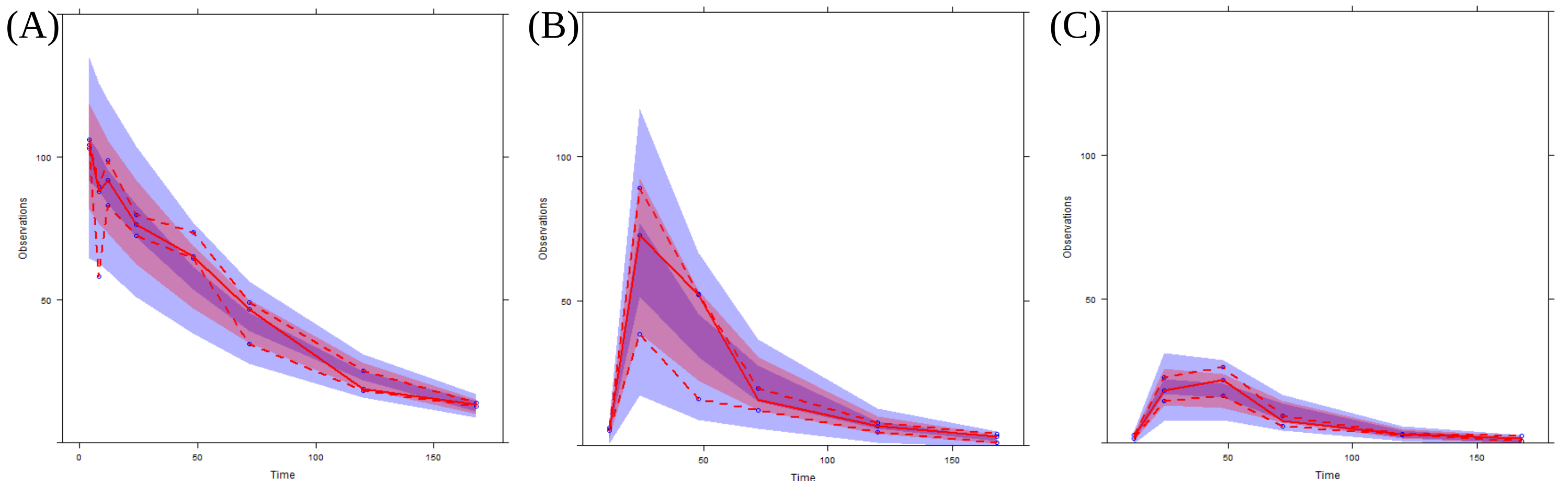


Figure1. Visual Predictive check of 1-step pharmacokinetic models(separated compartments) DV vs Time(hr)
(A) VPC of central compartment, (B) VPC of Rt Aqueous compartment, (C) VPC of Lt Aqueous compartment

◆ 2-STEP(multi-complex compartnets)

Table2. pharmacokinetic parameter value of 2-step(multi-complex compartment)

Parameter	Value
OFV	252.087
K _{AC}	0.0214
V _C	0.00164
K _{AR}	26.8
V _R	0.0156
V _L	0.0372
Q _R	0.00747
Q _L	0.503
CL	0.00033
M-time	12
Residual error	
Additive error	0.651
Propotional error	0.265

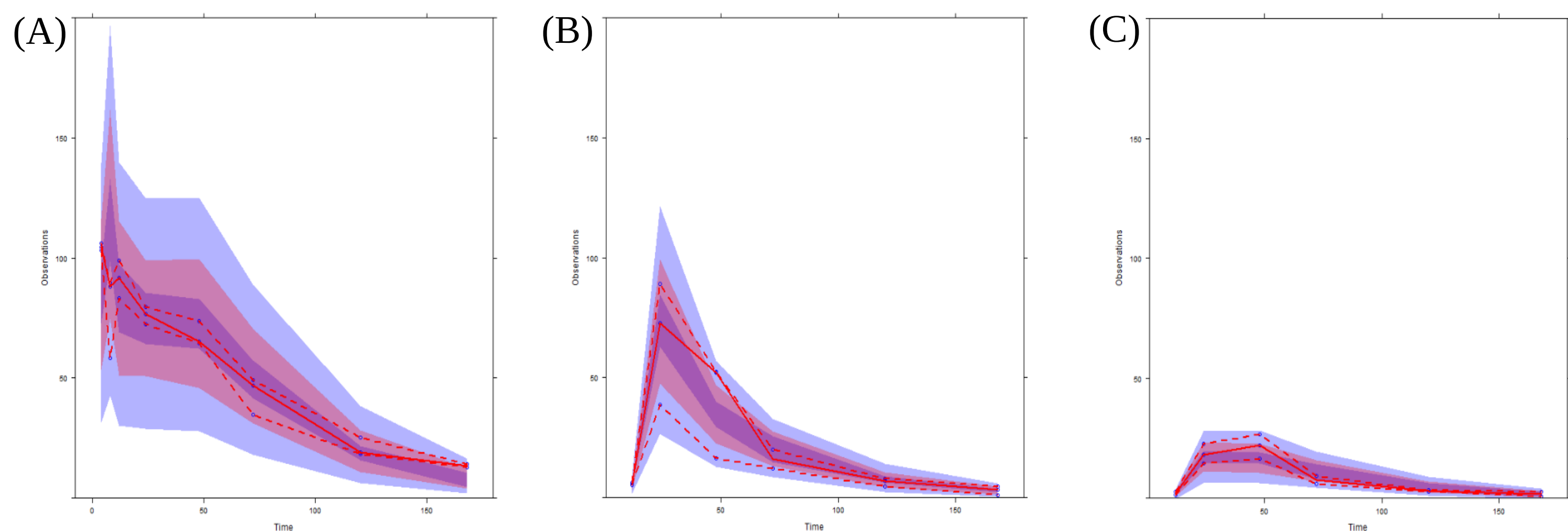


Figure1. Visual Predictive check of 2-step pharmacokinetic models(multi-complex compartments) DV vs Time(hr)
(A) VPC of central compartment, (B) VPC of Rt Aqueous compartment, (C) VPC of Lt Aqueous compartment

Conclusion

Subconjunctival injection pharmacokinetic model of bevacizumab shows both side aqueous (injected side and uninjected side) appeared bevacizumab. And two side aqueous have different concentration. Injected side has higher concentration than un-injected side. The parameters of each step pharmacokinetic model is very difference. But 2-STEP model has pharmacokinetic profile like raw data(pre-clinical test). This pharmacokinetic model(2-STEP) is simple and prediction is suitable. Therefore using this model, we can predict each side's bevacizumab concentration by blood sample.

Acknowledgement

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