Evaluating the Extent of Chemotherapeutic Contamination from Central Venous Catheters in Children with Cancer and Providing Guidance for Accurate Reporting of PK Parameters

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BACKGROUND

- Most children with cancer are treated with intravenous chemotherapeutics through an indwelling central venous catheter (CVL). PK sampling is collected via a separate peripheral intravenous line (PIV) to avoid drug contamination from the administration line. The discomfort and pain associated with the additional catheter requirement presents a major barrier for participation in pediatric PK studies.
- Actinomycin-D (AMD) and vincristine (VCR) are integral parts of chemotherapy regimen in childhood cancers. Their dose-toxicity relationships are poorly understood, and rational dosing information is scarce due to lack of PK data and PK study enrollment challenge.
- We recently developed a catheter clearing procedure that minimizes catheter contamination when a single CVL is used to administer and sample chemotherapy in children.

OBJECTIVES

- To support the use of the clearing procedure by applying modeling and simulation strategies to estimate the magnitude of residual contamination, develop an algorithm to ensure the accurate reporting of PK results, and evaluate the efficiency of the process for an ongoing BPCA clinical trial with AMD and VCR in pediatric cancer patients.

METHODS

I. Pilot Study

- Three pediatric cancer patients (ages 6, 14, 16 years) received AMD and VCR on a dose and schedule prescribed by their treating physicians.
- 4 (5, 30 min, 4, 20-24 hr) to 9 (5, 10, 30, 60, 90, 150 min, 4-6, 8-12, 20-24 hr) sets of PK samples were obtained from CVL and PIV.
- Catheter clearing procedure was applied prior to drawing the first and second samples from CVL.

1. Cook® 5 french 27 cm catheter fragment
2. 200 µL pipette tip
3. Cook® catheter syringe connector
4. Medex 3-way stopcock
5. Syringe for waste collection
6. Syringe for sample collection

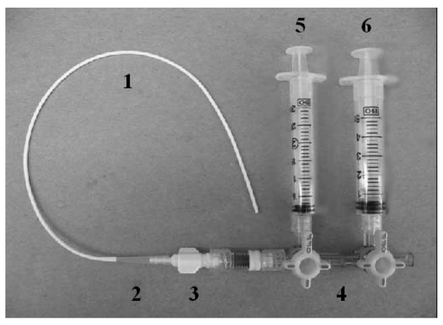
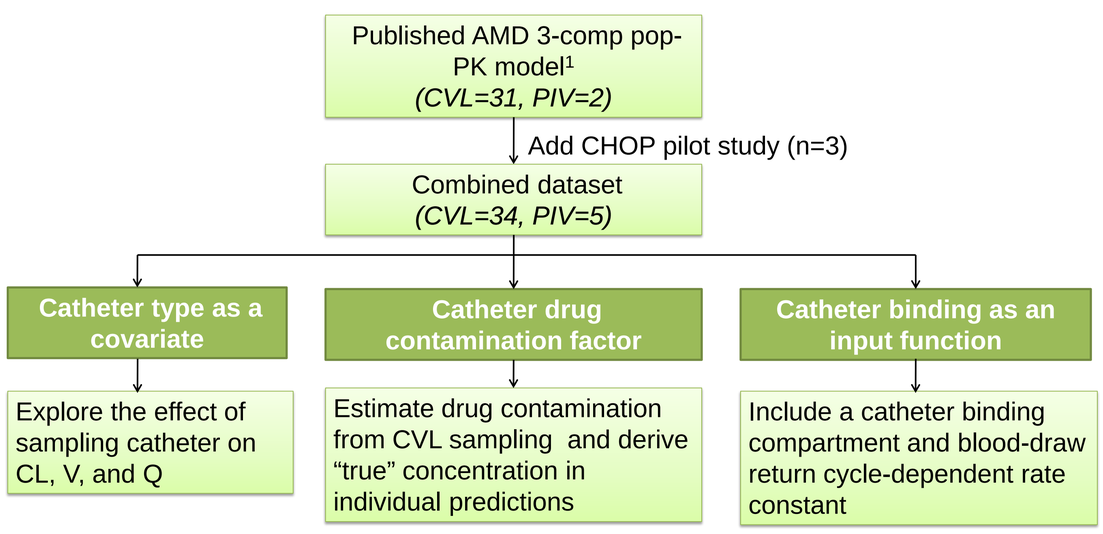


Figure 1. Schematic of the catheter clearing apparatus. Before the blood-draw, a 3-way stopcock was fitted to the catheter hub and 5 mL of blood was removed and returned to the patient for a total of 4 "pull-push" cycles.

II. Modeling Approaches

- Using a 3-compartment structural model (Mondick J. *et al. J Clin Pharm.* 2008; 48:35-42.), three approaches were evaluated to assess the effects of catheter contamination on AMD PK.



RESULTS

I. Catheter clearing procedure can efficiently reduce drug contamination from CVL sampling

- Residual contamination was observed for AMD but not VCR.
- The extent of contamination is time- and concentration-dependent.

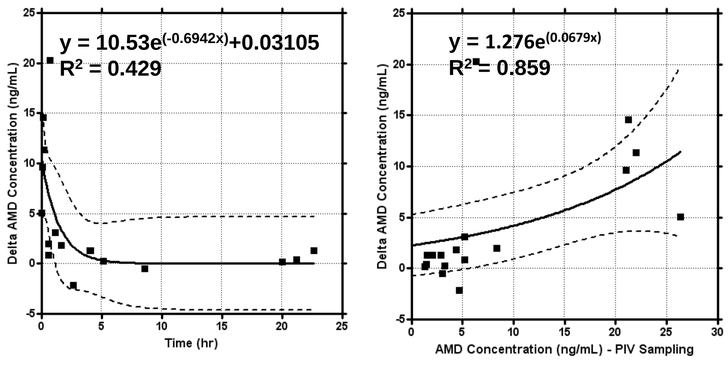


Figure 2. Discrepancy between CVL and PIV samples for AMD as a function of time and PIV concentration. Data was fitted with nonlinear exponential equation, plotted with the median and 95% confidence interval.

II. Modeling Approaches

- The combined AMD dataset contained 3 pediatric studies of 36 patients and 199 plasma concentrations.

RESULTS (continued)

Base Structural Model

- 3-compartment model with model parameters (V1, V2, V3, CL, Q2, Q3), inter-subject variability as exponential model on V1 and CL, residual proportional error model.
- Allometric normalized weight scaling (WT/70) for Vs (exponent = 1), CL and Qs (exponent = 0.75)

Catheter Covariate Model

- The effects of CVL sampling method can be applied as a power model on V1 and CL.

Baseline Contamination Model

- Assuming a baseline CVL contamination: **CTM = THETA*EXP(ETA)**, then **IPRED = F + CTM**
- Sensitivity analysis based on time and concentration indicated that CVL contamination should be accounted for when CVL DV ≥ 25 ng/mL.

Table 1. Summary of selected models

Model Structure	Δ Objective Function	Comments
$V1=\Theta1*(WT/70)*\Theta2^{CATH}$	-6.6	No covariance step, fixed V2,V3,Q2,Q3
$CL=\Theta3*(WT/70)^{0.75}*\Theta4^{CATH}$	-1.9	Terminated, fixed V2,V3,Q2,Q3
$V1=\Theta1*(WT/70)*\Theta2^{CATH}$ **$CL=\Theta3*(WT/70)^{0.75}*\Theta4^{CATH}$**	**-13.6**	Fixed Q2,Q3 **$V1=4.99*(WT/70)*0.843^{CATH}$** **$CL=20.3*(WT/70)^{0.75}*0.37^{CATH}$**
CTM=Θ5 on CVL, all times	-19.4	
CTM=Θ5 on CVL, time<1 hr	-47.1	
CTM=Θ5 on CVL, DV≥20 ng/mL	-71.0	No covariance step
CTM=Θ5 on CVL, DV≥25 ng/mL	**-69.2**	Minimized bias at mid-range **$V1=4.05*(WT/70)$** **$CL=12.1*(WT/70)^{0.75}$** **CTM=16.4 ng/mL (95%CI: 7.7, 25.1)**

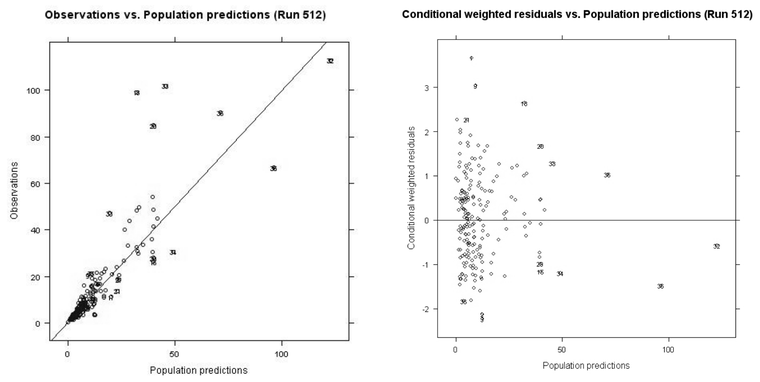


Figure 3. Diagnostic plots for the baseline contamination model.

Catheter Clearance Model

- Included a catheter depot and bound compartment, and leveraged parameter estimates from the *in vitro* study.

Parameter	Assumptions/ Initial Esitmates
F2: F unbound to central	0.76
F5: F bound in catheter	0.24
Fbound: F dissociated from bound	1.00
Kno: dissociation rate from bound	0.781 hr^{-1}
Krinse: dissociation rate with "pull-push"	1.67 hr^{-1}
K52 = Kno + Krinse*CYCL	

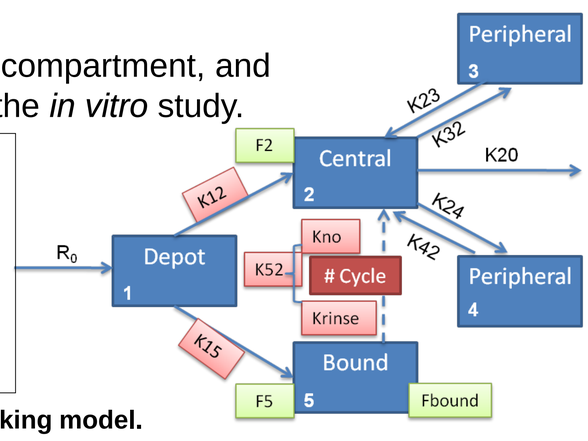


Figure 4. Schematic of the catheter clearance working model.

- Simulation indicates almost complete clearing of catheter-bound drug with 4 "pull-push" cycles after the 2nd sampling time. The model provides reasonable estimates of concentration from CVL sampling method, and simulated concentrations differ the most at early time points when "pull-push" catheter clearing is applied.

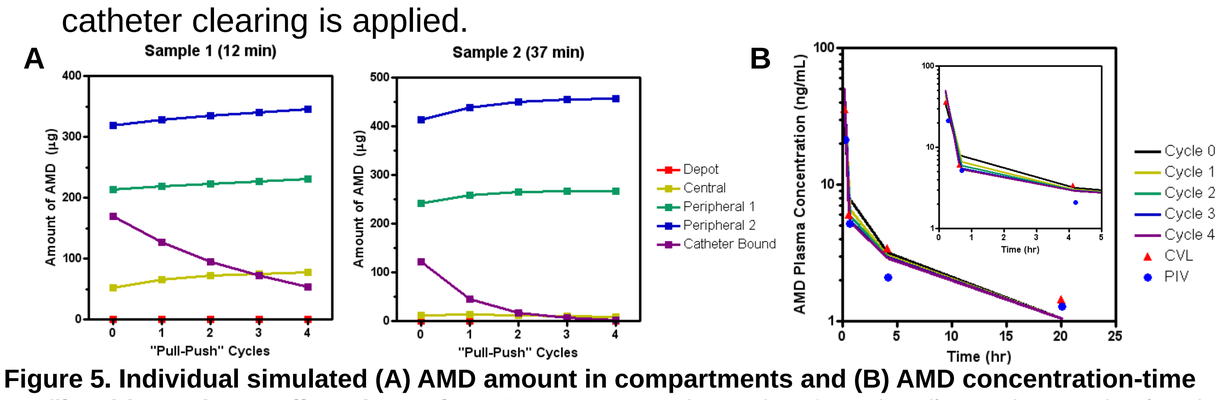


Figure 5. Individual simulated (A) AMD amount in compartments and (B) AMD concentration-time profile with varying "pull-push" cycles. One representative patient from the pilot study was simulated 100 times and respective medians were plotted.

CONCLUSION

The catheter clearance model supports the use of the clearing procedure during PK sampling from a single central catheter at early time points. Although it is more robust in depicting catheter kinetic processes, the model is highly parameterized for the limited dataset. The catheter baseline contamination model provides a more simplified approach with fewer assumptions regarding binding phenomenon or catheter geometry and provides equitable estimates for predicted "corrected" plasma concentrations at early time points.