Pharmacometrics-based Design and Analysis of Pediatric Trials

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Pharmacometrics is the science that deals with quantifying pharmacology and disease through modeling and simulation of data to influence drug development and regulatory decisions.

Synonyms: Modeling&Simulation, PKPD, Exposure-Response, Concentration-effect relationships

Argatroban Injection in pediatrics (birth to 16 yrs)

Pharmacometrics-based Dosing Recommendations

NDA 20883/S014

Argatroban

- Synthetic Direct Thrombin Inhibitor
- Approved in Adults
  - prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT)
  - Anticoagulant in Percutaneous coronary intervention (PCI) patients with HIT or at risk for HIT
- Adult Dosing
  - Initial dose in HIT: 2 mcg/kg/min
  - Titrated to 1.5 – 3 times baseline aPTT (not to exceed 100sec) at steady-state (1 – 3 hrs)

Pediatric PKPD Data

- 15 of the 16 patients received 6-10 doses of argatroban over 14 days.

- Serial concentration and aPTT measurements were available in each patient. In total, about **166 concentration** and **329 aPTT** measurements were available over a concentration range of **100 to 10,000 ng/mL**.

Healthy adult PKPD data were available

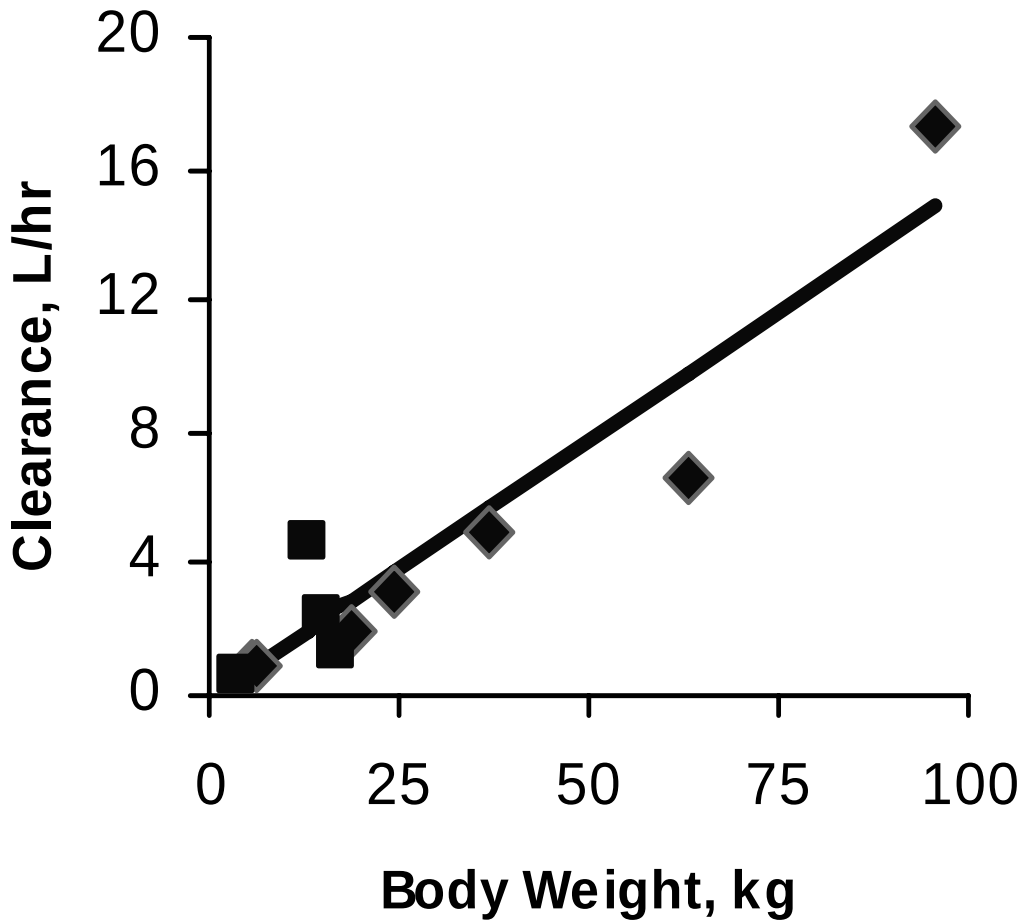
- Argatroban plasma concentration and aPTT data from 5 healthy adult studies (N=52) were used for model development.

- Infusion doses range from 1µg/kg/min – 40µg/kg/min

Pharmacometrics Approach

- Analyze PK: Dose - Argatroban concentration relationship; understand intrinsic/extrinsic factors influencing PK
- Analyze PD: Concentration – aPTT relationship
- Find Optimal Dosing: Use concentration – aPTT and PK models to explore competing dosing schemes

Body weight reduces the between-patient variability from 70% to 41%



Patients with elevated bilirubin exhibit 75% lower clearance (CL) than normals

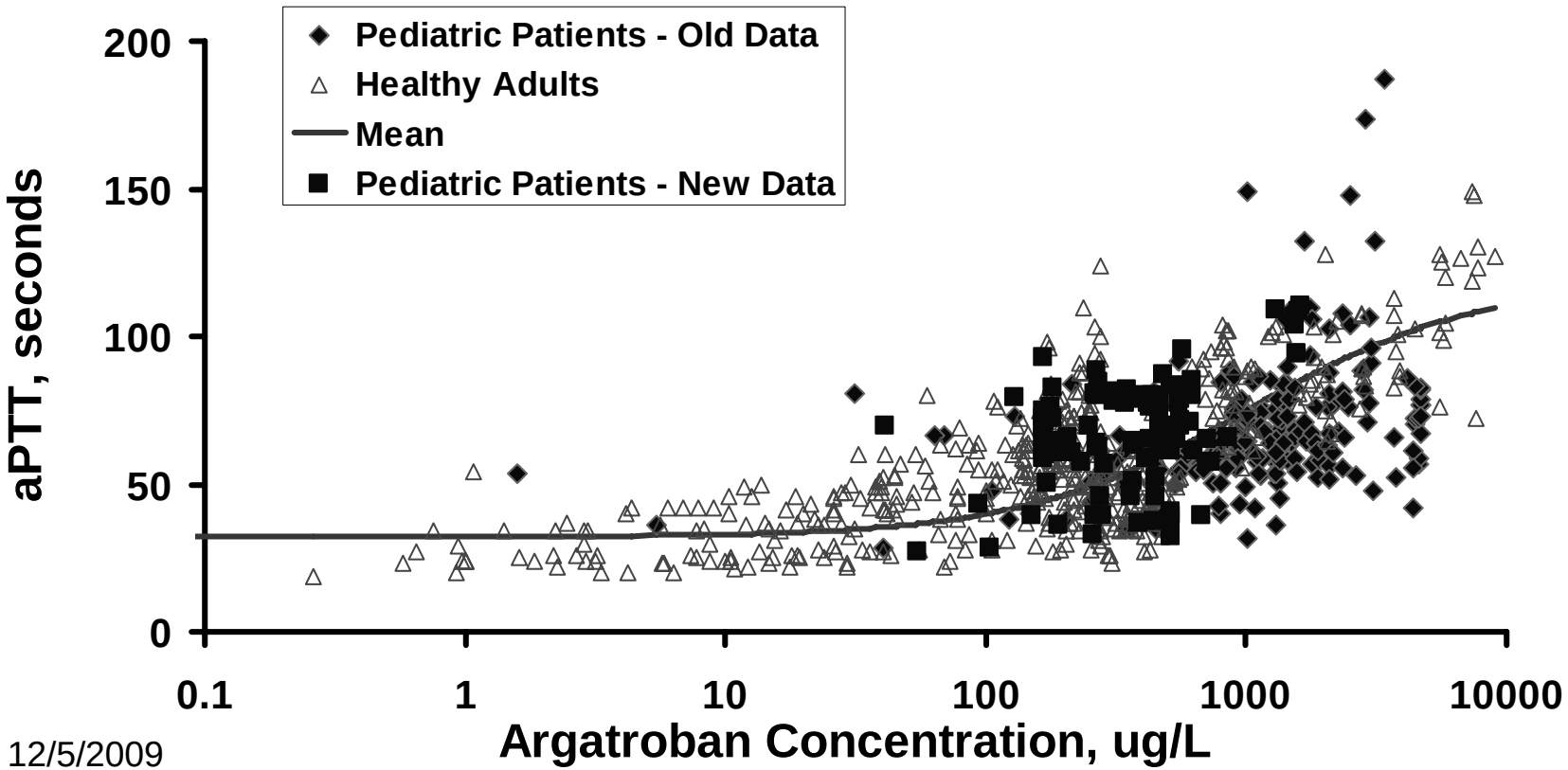
Variability reduces further to 30% upon adjusting for hepatic status, after body weight

	Patients with normal bilirubin (N=11)	**Patients with elevated bilirubin (N=4)**
CL, L/hr/kg	**0.17**	**0.04**

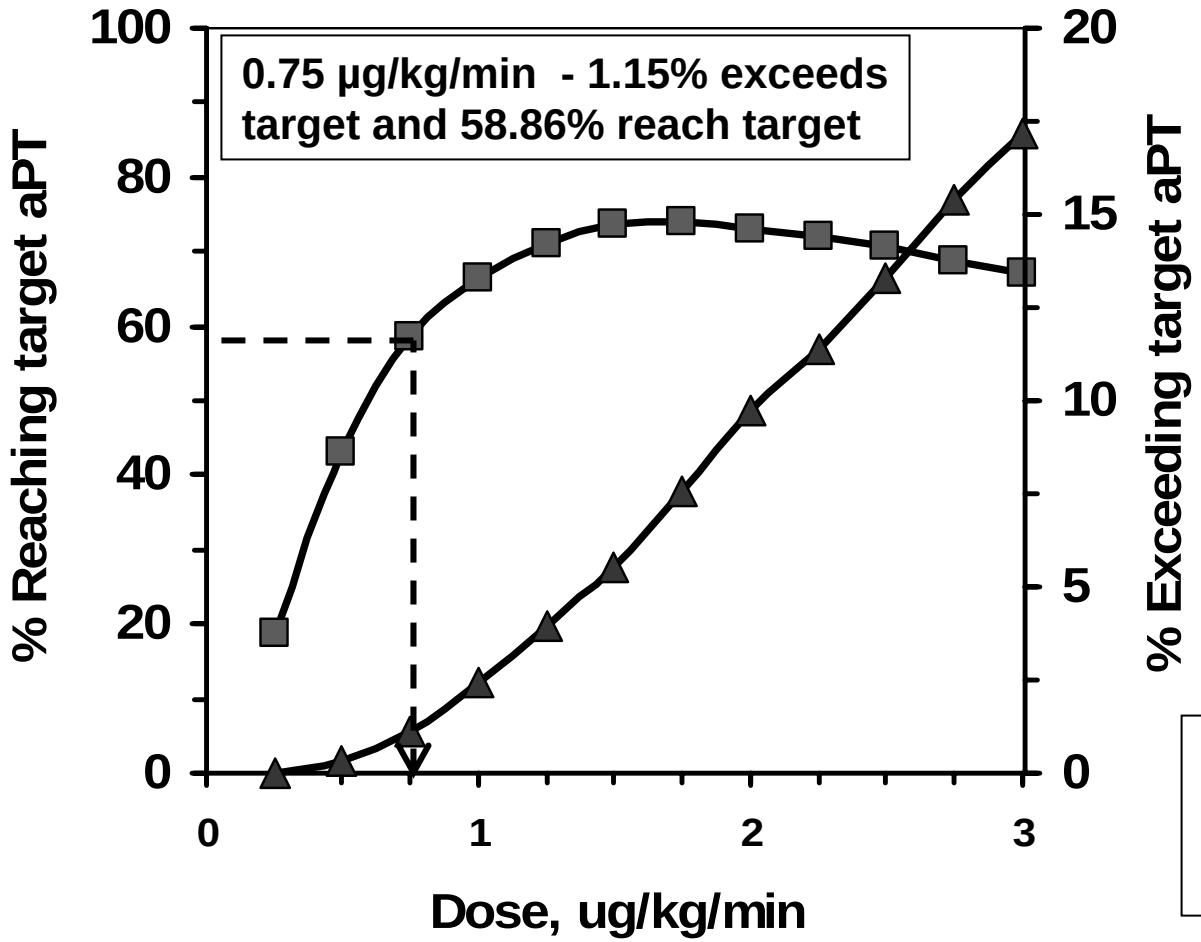
Elevated bilirubin was manifested by cardiac complications

Effect on aPTT is concentration dependent

Concentration-aPTT relationship is similar between adults (healthy) and pediatrics (patients)



0.75 µg/kg/min in pediatrics is a reasonable starting dose

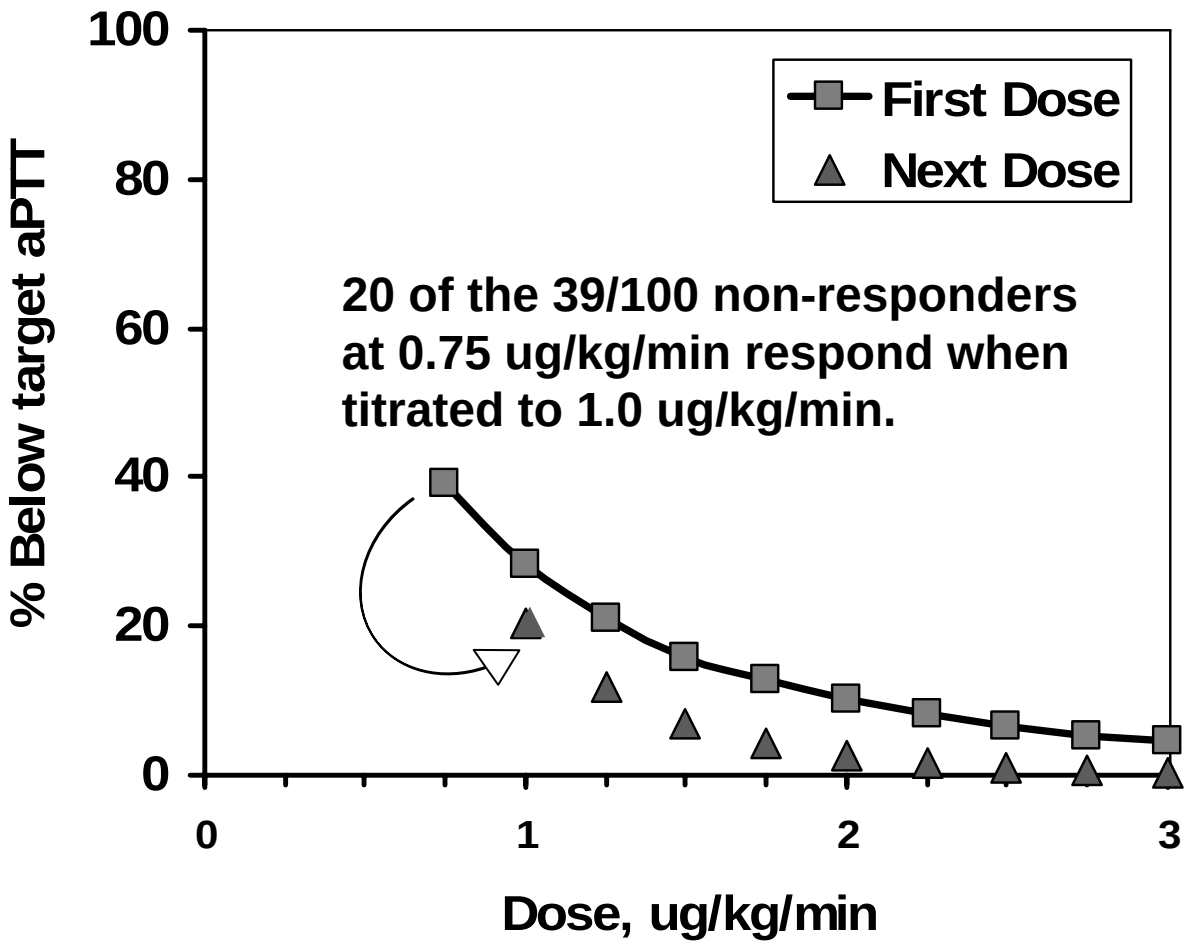


Target: 1.5-3 times baseline aPTT and < 100 seconds.

In adults, the approved starting dose is 2 µg/kg/min and the max dose is 10 µg/kg/min. This starting dose results in 1.92% exceeding & 66.9% reaching target aPTT.

0.25 µg/kg/min is a reasonable incremental dose

No additional anti-coagulation beyond 3 ug/kg/min



Key Findings

- PK in pediatric patients (N=10) is well characterized
- Exposure-Response (aPTT) relationship well characterized in pediatric patients
  - Starting dose of 0.75 ug/kg/min, titrate to effect in increments of 0.25 ug/kg/min every 2-4 hrs.
  - In patients with impaired hepatic function the starting dose is 0.20 ug/kg/min, titrate to effect in increments of 0.06 ug/kg/min.

Steps to improve pediatric trials '*Learn-Apply*'

- Use prior dose-response from adults and related pediatric effectiveness/safety trials to design future trials
  - All pediatric trials are required to be justified using pharmacometrics-based modeling and simulation.
  - Where applicable, pediatric trials are required to be designed to estimate mean PK parameters with a 20% confidence interval
  - Analyze all pediatric trials for exposure-response

References

Regulatory Application of Pharmacometrics Analyses

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