Use of Pediatric and Adult Midazolam Population Pharmacokinetics to Assess IM Dosing and Early Drug Exposure for Status Epilepticus

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DISCLOSURE STATEMENT

Edmund Capparelli (Presenter)

Dr. Capparelli has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

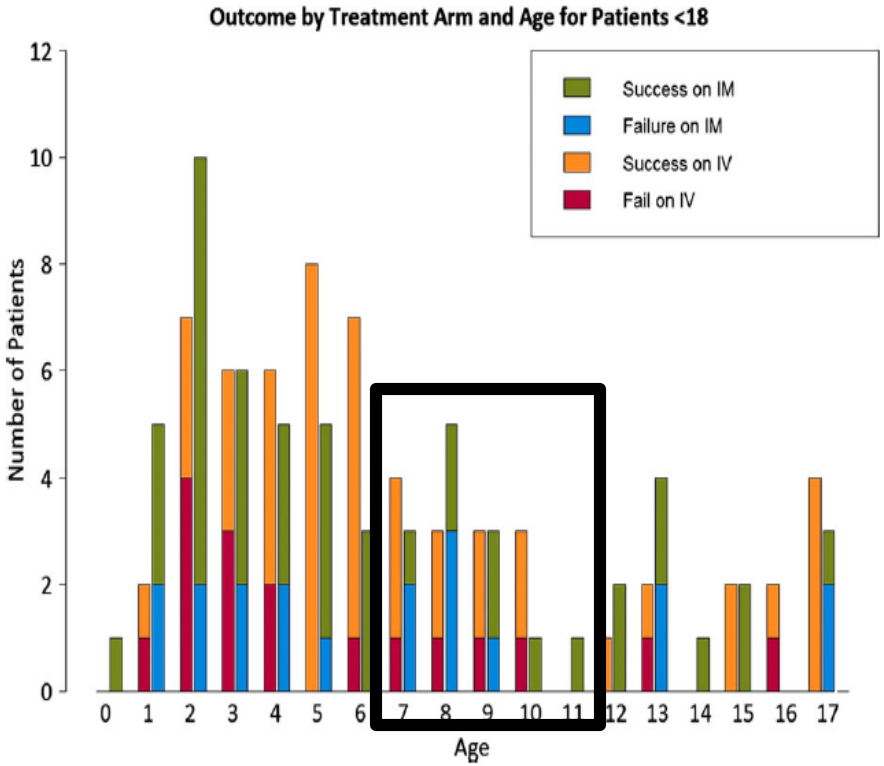
Affiliation / Financial Interest	Organization
Consultant	Alexion, Gilead
DSMB Member	Cempra, The Medicines Company

Background

- IM midazolam (MDZ) is an attractive option for treatment of status epilepticus (SE).
- Fixed IM doses using as auto-injectors (IMA) allows rapid administration and provides consistent dosing in adults.
- However IMA have limited flexibility for pediatric dosing on a mg/kg basis.
- The RAMPART Study of adults and children (>13kg) demonstrated MDZ by IMA is at least as safe and effective as intravenous lorazepam for pre-hospital seizure cessation (R Silbergleit et al NEJM 2012)

Pediatric RAMPART

- Sub-analysis performed in 120 pediatric RAMPART subjects: MDZ IMA (n=60, age 6.4 ± 4.8yr) LRZ IV (n=60, age 6.9 ± 4.6yr)
- Most MDZ subjects (49/60) received 5mg dose
- Only 5 (8%) MDZ subjects required intubation.
- MDZ found to be non-inferior – Success: MDZ 68% vs LRZ 72.%
  - Success in 7/13 (54%) of 7- <12 yr olds (presumed 5mg dose)



R Welch et al Epilepsia 2015

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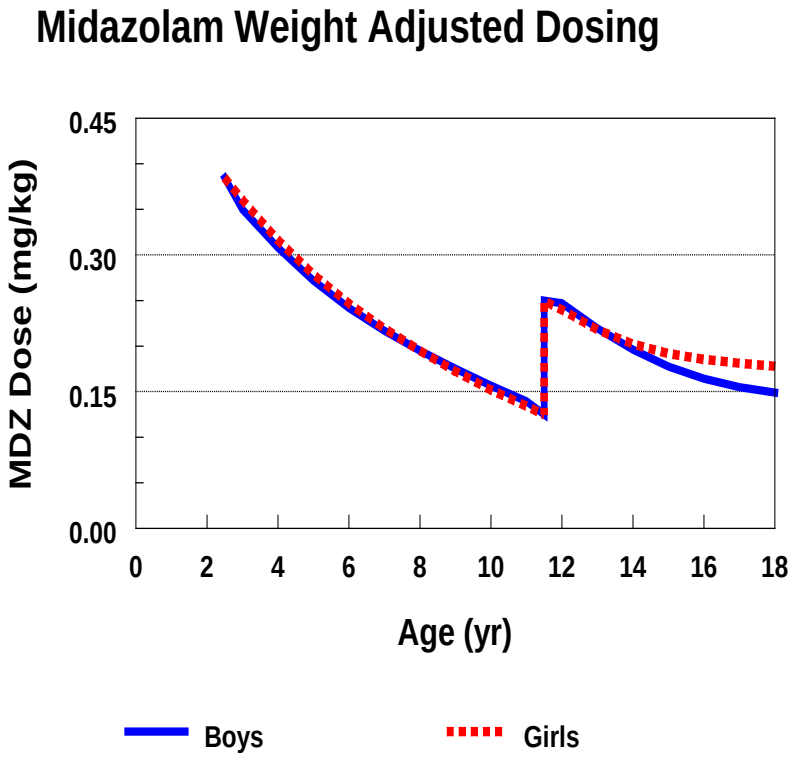
RAMPART MDZ Pediatric Dosing

- RAMPART MDZ IMA Dosing:
  - 5 mg (13-40kg)
  - 10 mg (>40kg)
- RAMPART MDZ IM dose also recommend in AES “White Paper” (Glauser et al Epilepsy Cur 2016)
- Weight normalized MDZ Dosing:
  - 0.125-0.385 mg/kg – a 3.1 fold range in dosage
- MDZ PK not evaluated in the RAMPART Study



Objectives

- To develop a population PK model to describe midazolam pharmacokinetics in adults and children with various routes of administration
- To use Monte Carlo simulate pediatric exposures following IM administration using RAMPART dosing

Methods – Data Sets

Study PI	Population	Number of Subjects	Route of Administration
S. Muchohi	Peds	20	IV (n=9) / IMNS (n=11)
M. Reed	Peds	32	IV
J. Barrett	Peds	264	PO
E. Jacquz-Aigrain*	Peds	23	IV
S. deWilt*	Peds	42	IV (n=24) / PO (n=18)
Alfonzo-Echeverri	Adult	10	IMNS
Dept of Defense	Adult	135	IMA
J. Ma	Adult	153	IV (n=54) / PO (n=88) / IV & PO (n=11)
TOTAL		**614**	**IMM (n=21) / IMA (n=135) / IV (n=106) / PO (n=352)**

*Studies of subjects < 13kg and data not included not final PK model for simulation of RAMPART dosing

Methods: Population Pharmacokinetic Analysis

- Concentration-time data were analyzed with nonlinear mixed-effect modeling using NONMEM version 7.2
- Clearance was scaled by allometric weight ($WT^{0.75}$) and volume of distribution was scaled by weight ($WT^{1.0}$) prior to evaluation of potential impact of age and study effects.
- Covariate impact determined by univariate screen followed by multivariate backwards elimination analysis.
- IM absorption – by method IMA vs IM Needle/Syringe (IMNS)
  - Applied to Bioavailability (F) and Absorption Rate Constant (KA)
  - 1000 sample bootstrap used to determine parameter confidence intervals (Wings ver 7.4)
- Final PK model was used to perform Monte Carlo simulations

Methods: Monte Carlo Simulations

- The final Population PK model was used for Monte Carlo simulations with the RAMPART dose
  - 13-40 kg – 5 mg IMA
  - >40 kg – 10mg IMA
  - Virtual Subject Characteristics
    - Age uniform distribution at 2.5 yr, every year 3-18 and adult
    - Males 50% / Females 50%
    - Weights – CDC-NHaines median values for pediatric – 70kg for adults
    - 100 replications for each age (yr), sex group (M/F)
    - Grouped by Age: 2-6, 6-12, 12-18 yr and adult
  - Frequency of MDZ concentrations <40, 40-200 and >200 ng/mL at 10, 15, 30, 45 and 60 minutes determined.

Results – Population PK Model

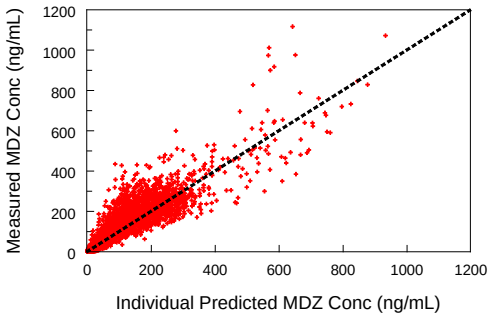
Typical PK Parameters

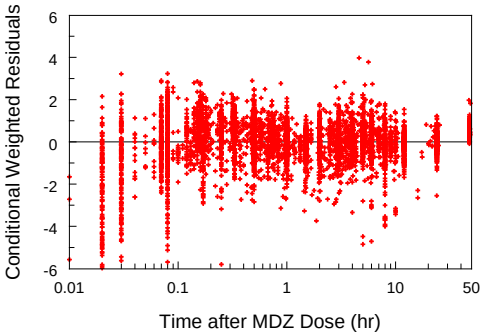
- Vc = 0.288 L/kg (Age<13yr)
  - 0.483 L/kg (Adults)
- CL= 30.7 L/h $(WT/70)^{0.75}$

(0.67, 0.50, 0.44 L/h/kg at 13, 40, 70kg)

- Vp= 1.06 L/kg
- KA = 0.692 hr^{-1} (IMA)
- F =0.976 (IMA) $(weight/70kg)^{0.75}$

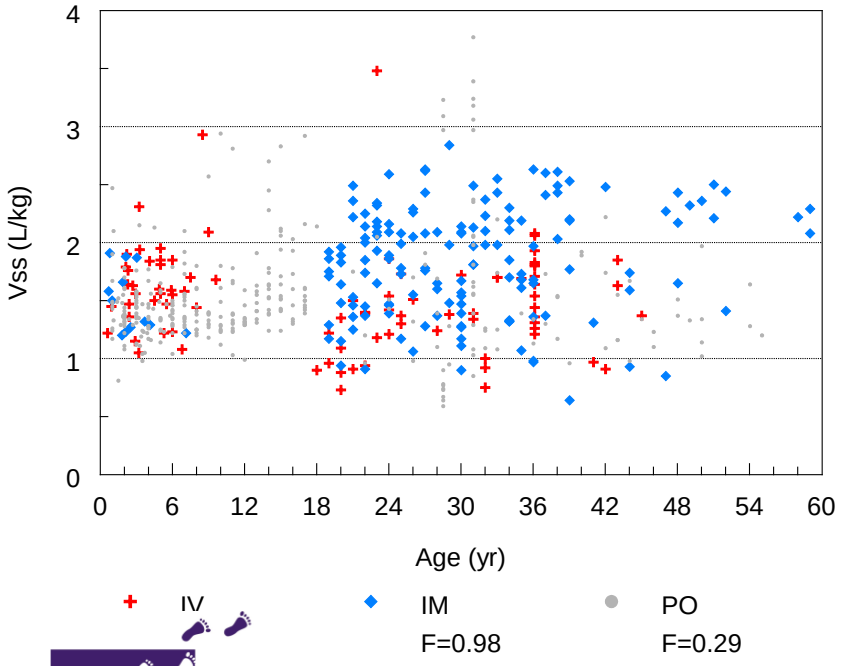
Goodness of Fit Plots



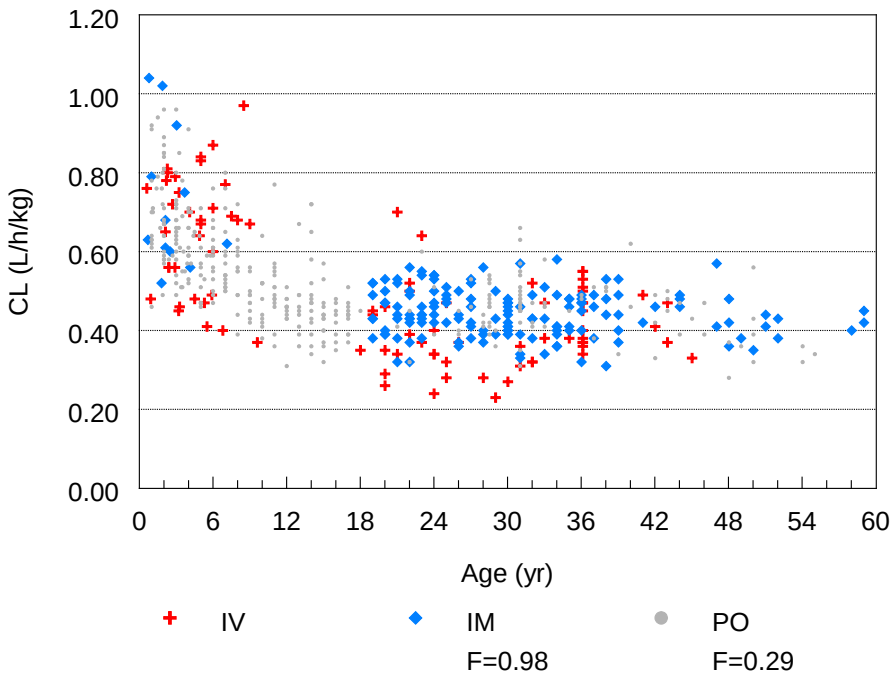


Influence of Age on Midazolam Pharmacokinetics

Volume of Distribution (Vdss)



Clearance (CL)



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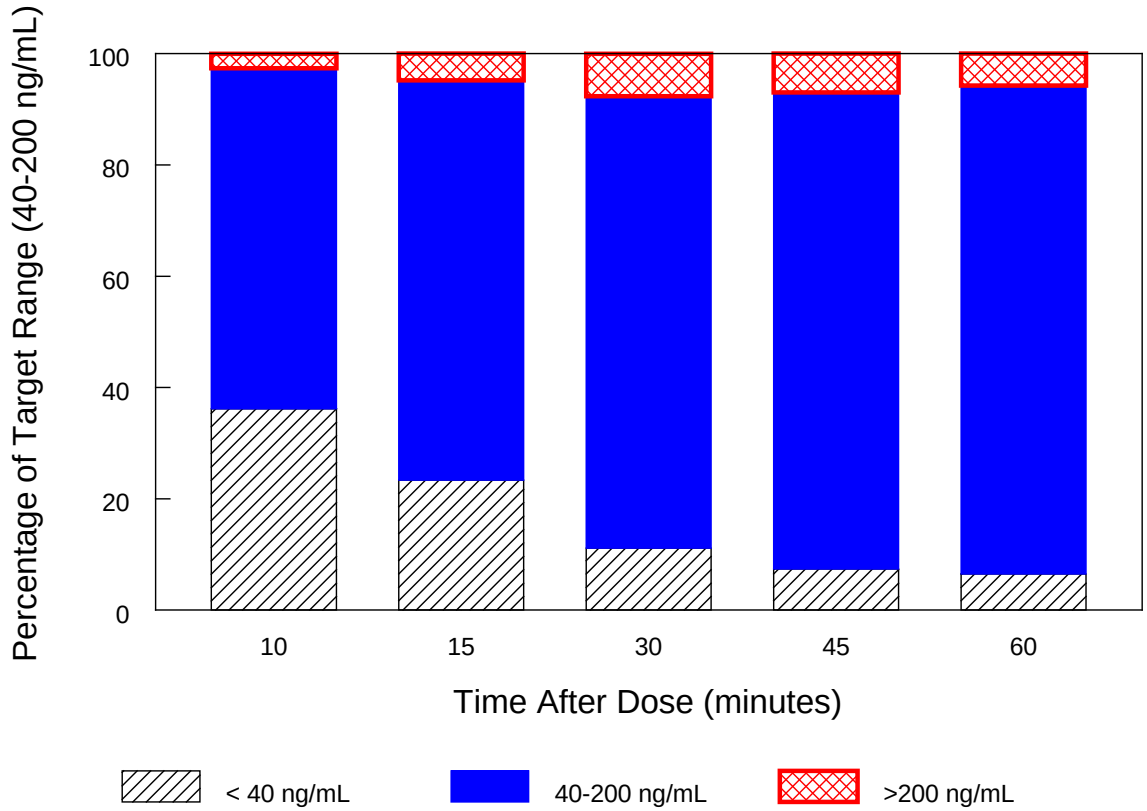
Midazolam IMA Pediatric Target Achievement Over the First Hour



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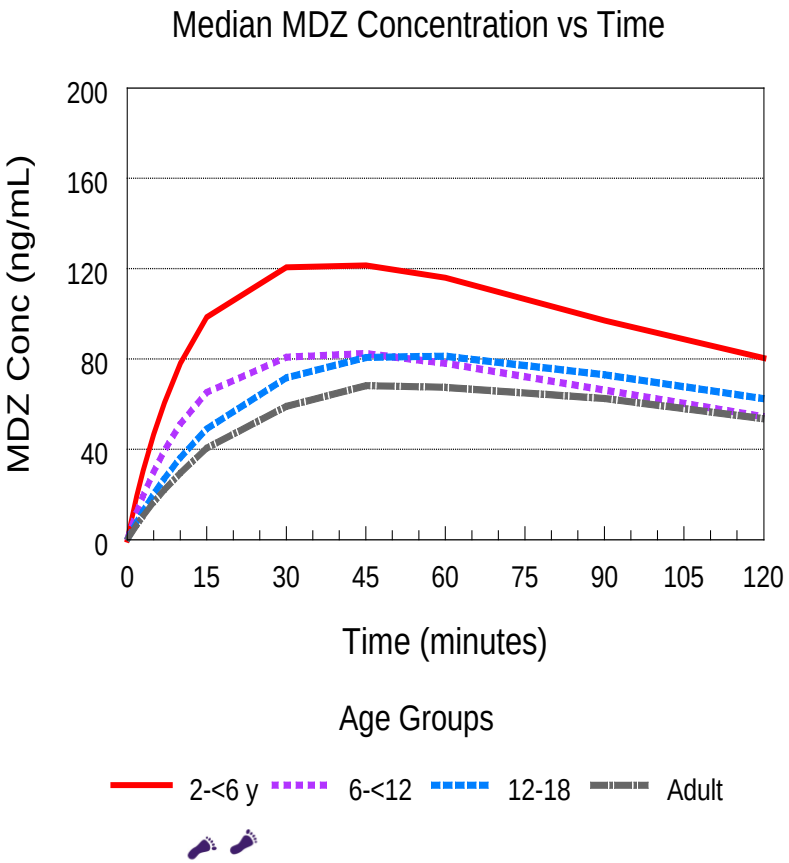
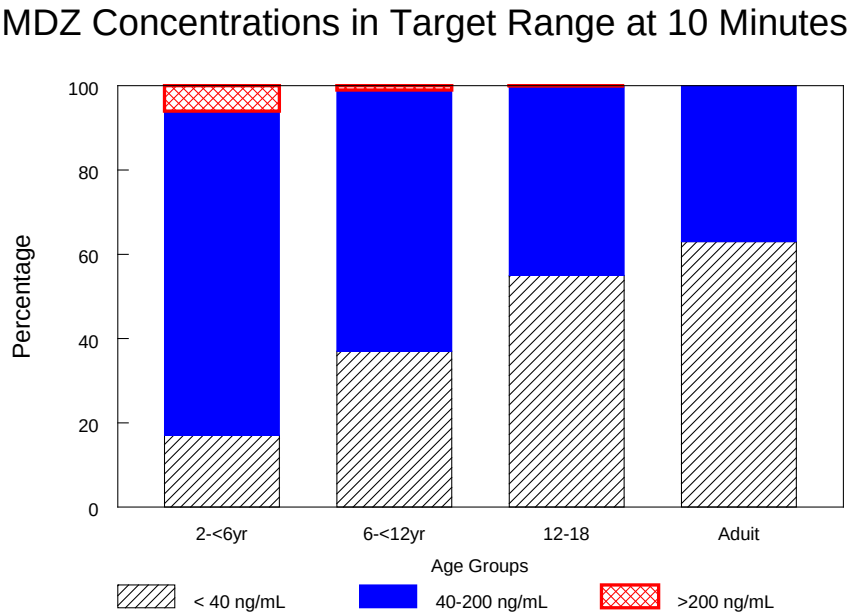
Midazolam IMA Concentrations: Impact of Age





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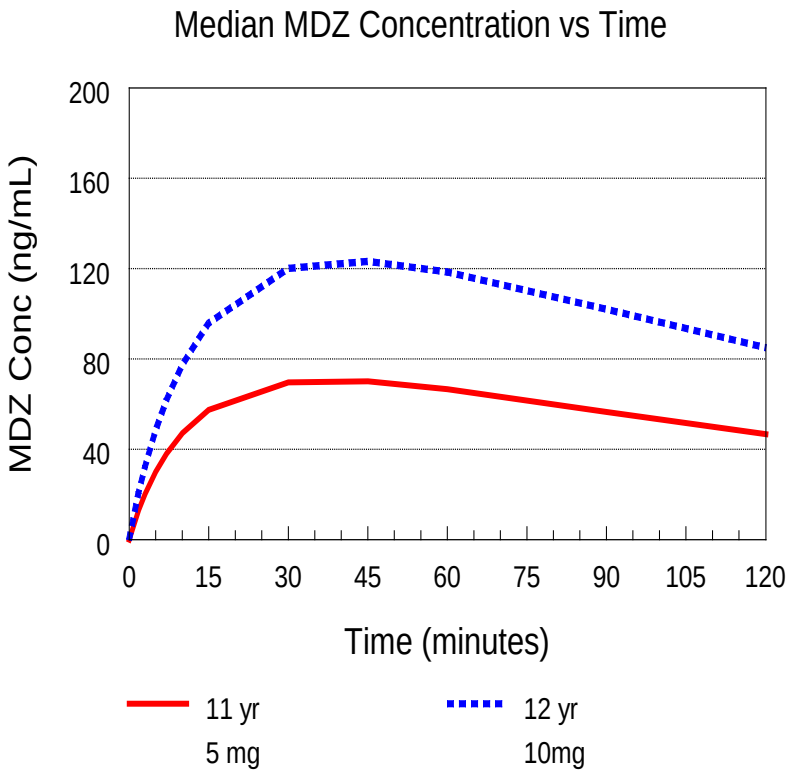
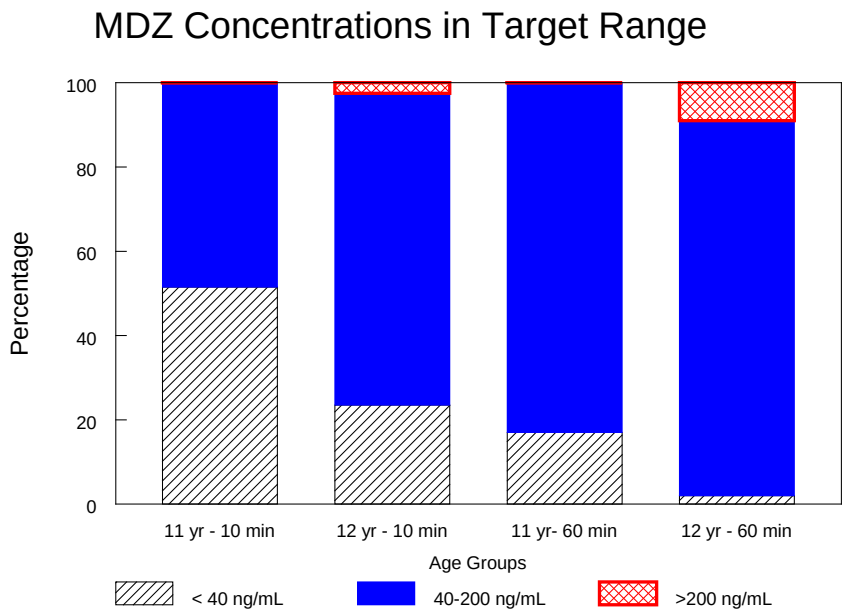
Midazolam Concentrations Around IMA Dose Increase





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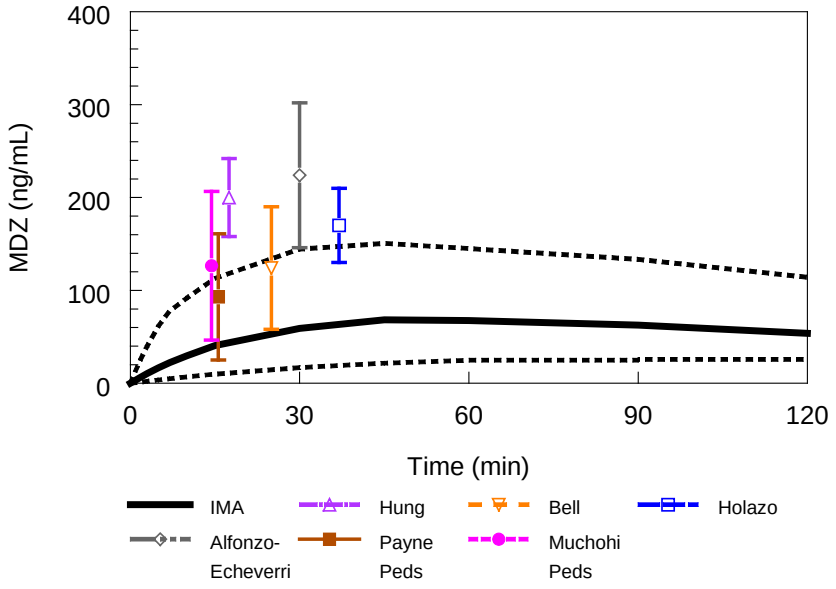
Midazolam PK: IMA vs IMNS

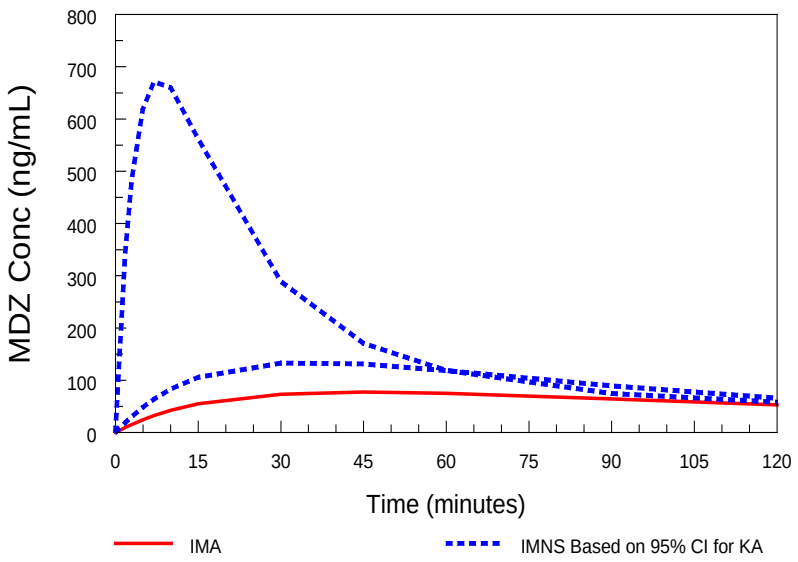
- Literature IMM vs DOD IMA
  - Cmax higher
  - Tmax quicker
- Population PK Model
  - Raw IMM data only 21 subjects
    - Pediatric IMNS– limited early sampling
    - Adult IMNS – GS/MS assay
    - Bootstrap Assessment of IMNS Absorption
      - KA (95% CI) – 9.1 (1.2-15.0) hr^{-1}
      - F (95% CI) – 1.39 (1.18-1.99)

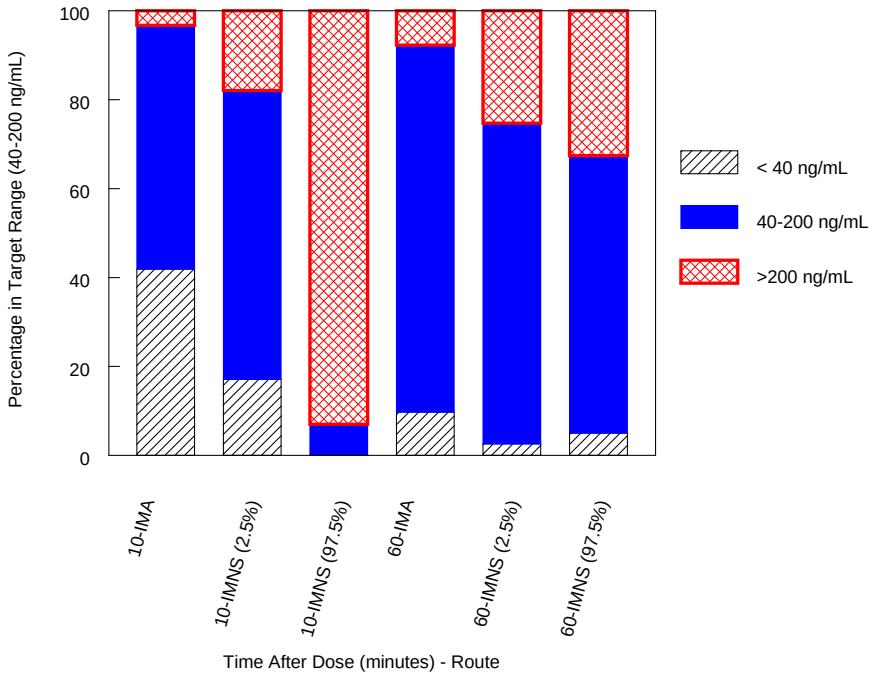
PK Comparison of MDZ IMA (DOD) to IMNS (Literature)



Dose normalized to 10mg (0.15mg/kg)

Midazolam PK: IMA vs IMNS Administration Using 95% Limits for IMNS KA / F





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Conclusions

- MDZ concentrations in the first 5 minutes after IM administration are highly variable
- Therapeutic MDZ levels are expected rapidly with IMA administration in using RAMPART dosing in children and adults.
- Higher initial MDZ concentrations are encountered with IMNS vs. IMA administration but are similar 1-1.5 hours post administration.
- While higher MDZ concentrations are predicted in young children (2-6 yr) compared in older populations with RAMPART dosing, MDZ concentrations > 200 ng/mL are rarely expected with IMA.
- Due to more rapid absorption and higher initial concentrations with IMNS administration a mg/kg dosage may be preferable in smaller children.