Population Pharmacokinetics of Intravenous Busulfan in Children

- Comparison with Oral Busulfan-

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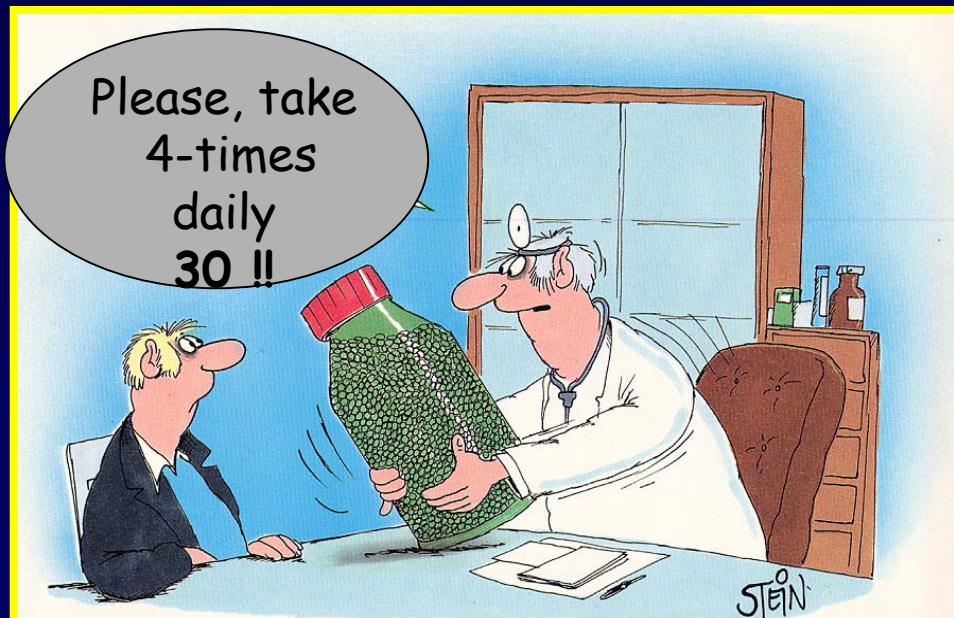
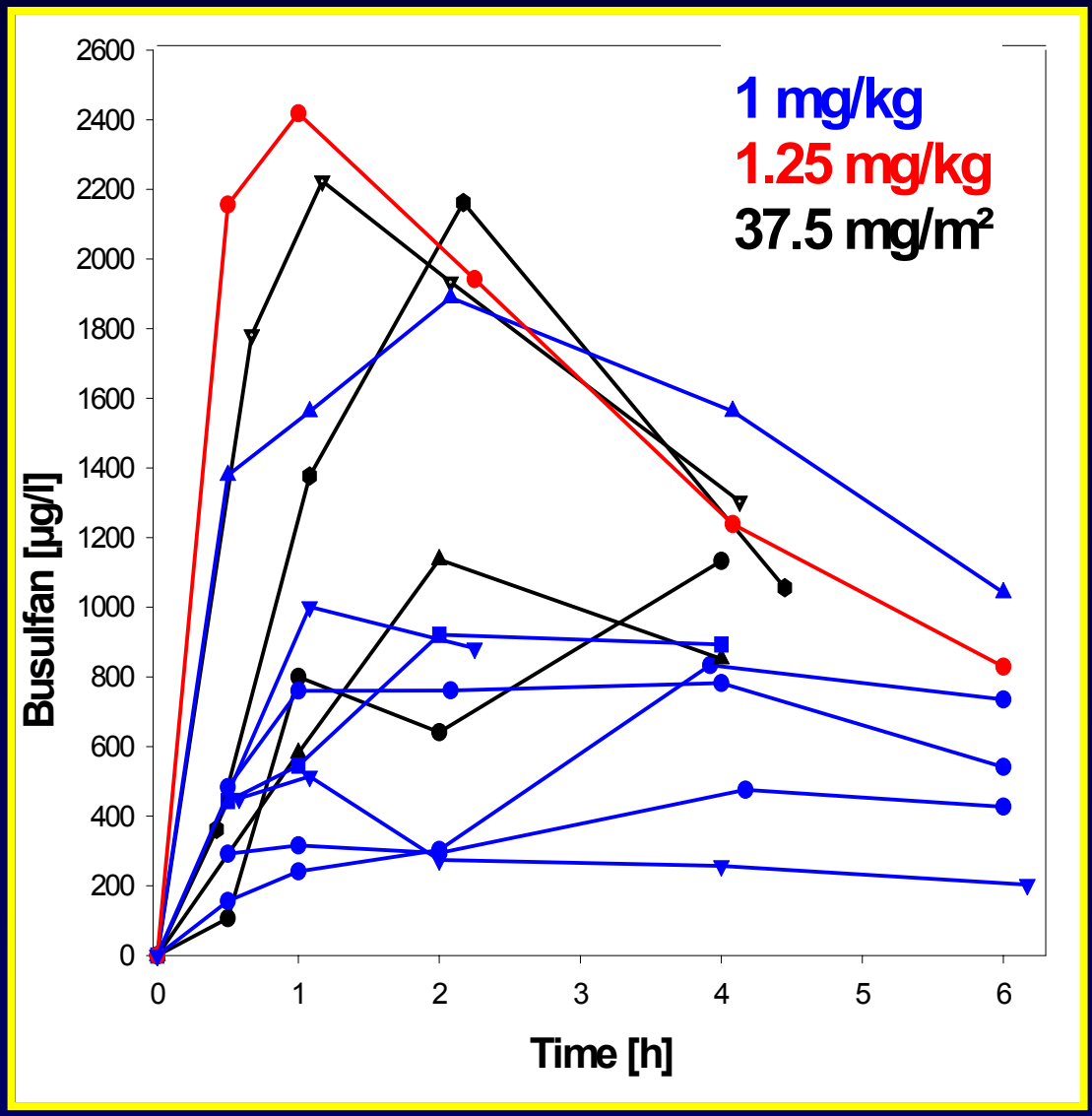
Supported by BMBF (#01EC9801)

Oral Busulfan in Children

- High-dose chemotherapy prior to bone marrow transplantation (BMT); *off-label use*
- Standard dose: 1mg/kg or 37.5 mg/m^2 q6h x 16 doses
- AUC correlates with the incidence of veno-occlusive disease (VOD)
- Dosage form:
  2 mg- tablet (Myleran®)
- Problems with swallowing!



Busulfan Disposition Curves after Oral Application



→ High variability AUC

→ Acc. to Vassal et al.[1]:

n = 27 children

AUC = 1581 ± 587 µM x Min

CV = 37%

[1] Vassal et al, Blood 79: 2475-79, 1992

A Population Analysis of Oral Busulfan
- 48 Children -

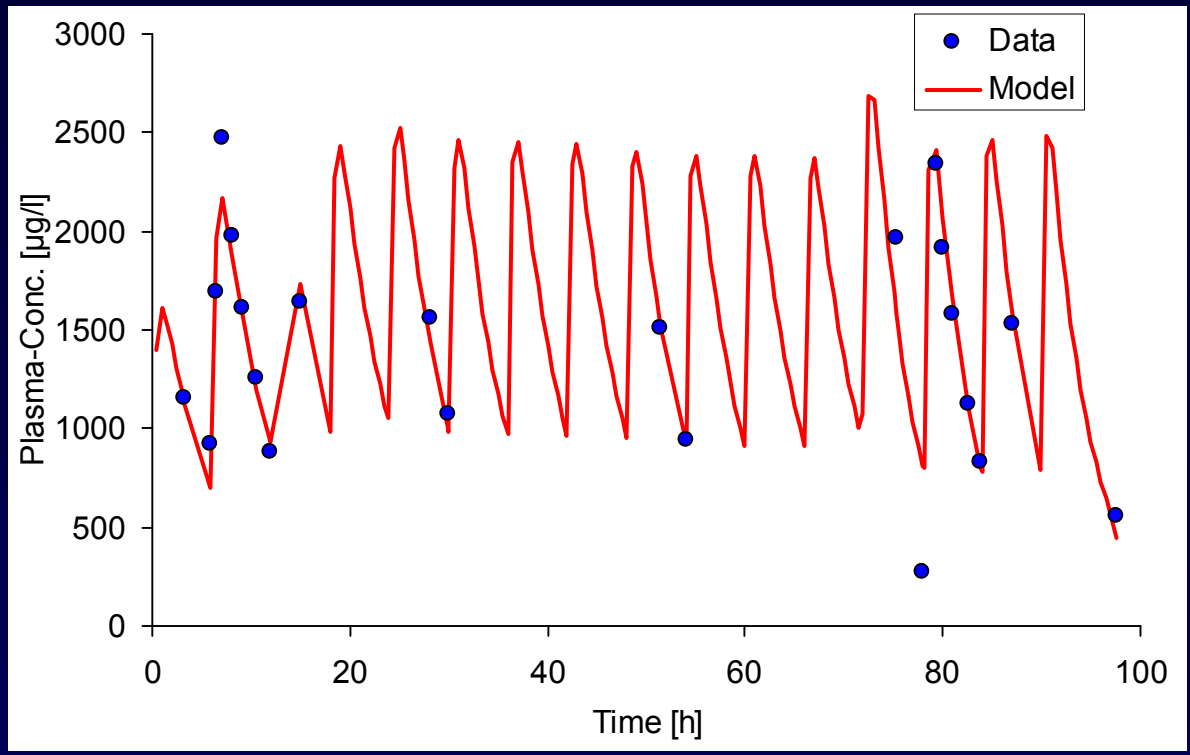
	Mean (CV)	Median	Range
Age (years)	9.9 (48%)	10.4	0.4 - 18.1
Weight (kg)	37 (52%)	34	5.49 - 80
BSA (m^2)	1.2 (38%)	1.15	0.29 - 2
Height (cm)	137 (24%)	144	56 - 185
Dose (mg)	37.9 (49%)	40	5 - 80

Hospital	No. of patients	Busulfan assay	No. of samples (total)	Samples per administration	Samples per patient (mean over 4 days)
Jena	13[a]	LC-MS (assay 1)	52	1	4
Tübingen	20[b]	LC-MS (assay 2)	1 - 8	1 - 8	17
Münster	15[a]	HPLC-UV (assay 3)	1 -5	1 - 5	7

a = patients received clonazepam (0.09 mg/kg/d)
b = patients received phenobarbital (5 mg/kg/d) as anticonvulsive prophylaxis

Population Pk of Oral Busulfan in Children

(NONMEM, FOCE, 1-Comp.-Model, additive & proportional error model)



	Population Mean	Interindividual Variability	Intraindividual Variability
Cl/F (l/h/m^2)	**4.13**	26%	10%
V/F (l/m^2)	**21.3**	31%	20%
ka (1/h)	**1.31**	110%	----

residual error: 123 µg/l / 14.9% for Jena/Münster pts., 192 µg/l / 23% for Tübingen pts.

Population Pk of Oral Busulfan in Children

		Population Mean	Range	Interind. Variability
This work*	Cl/F (ml/min/kg)	2.42	1.42-5.46	26%
n=48, 0.4 to 18.1 y	V/F (l/kg)	0.73	0.38-1.62	31%
	ka (1/h)	1.31	0.18-10,92	110%
Sandström et al. **	Cl/F (ml/min/kg)	4.98	1.97-8.93	41%
n=12, 1.3 to 12 y	V/F (l/kg)	0.96	0.50-1.57	36%
	ka (1/h)	4.99	1.12-19.1	131%

**Schiltmeyer B et al, Cancer Chemother Pharmacol, in Press*
***Sandström et al., Bone Marrow Transplantation 2001; 28:657-664*

- high variability in ka
- no age-dependent clearance
- no influence of phenobarbital on Busulfan clearance
- Body surface area slighty better predictor of Cl than weight

Intravenous Busulfan (Busulfex®)

- approval in US: Conditioning regimen prior to BMT
- Contains Dimethylacetamide (DMA) as a solvent
  - hepato- and neurotoxic

Clinical study with primary endpoints

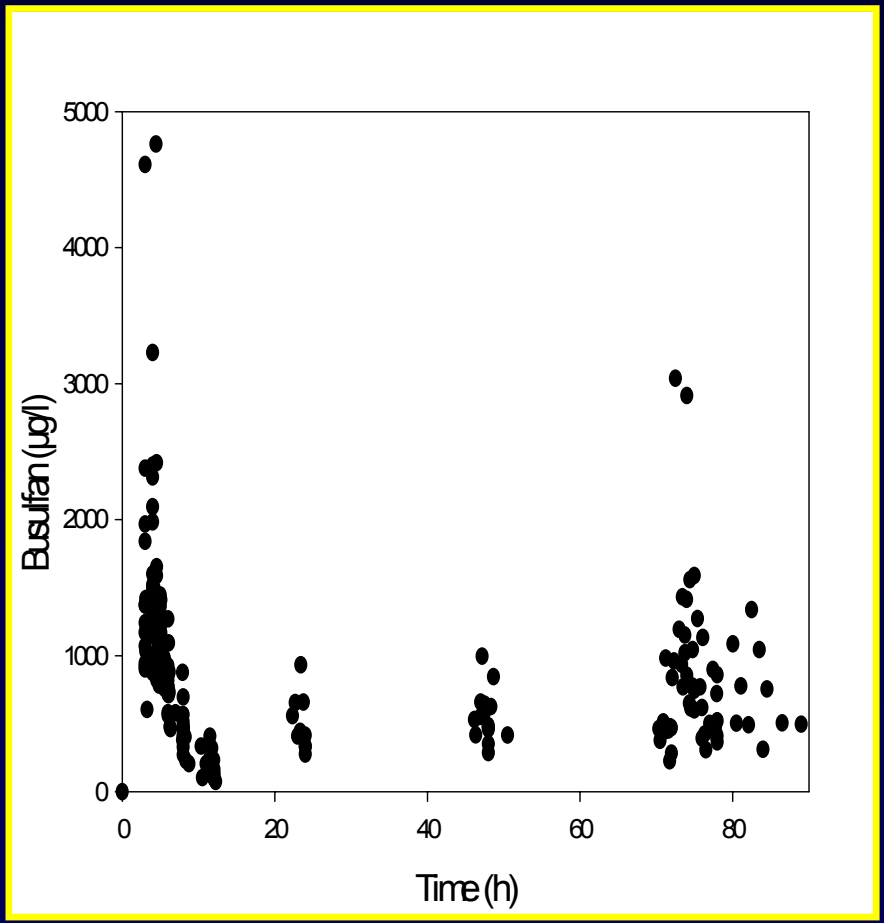
- Target AUC of 1600 ± 600 µM x Min
- Lower variability of AUC ($\Rightarrow$ CV of AUC equal to or smaller than the CV with oral administration = 37%)
- Documentation of toxicity

Study Design and Patients

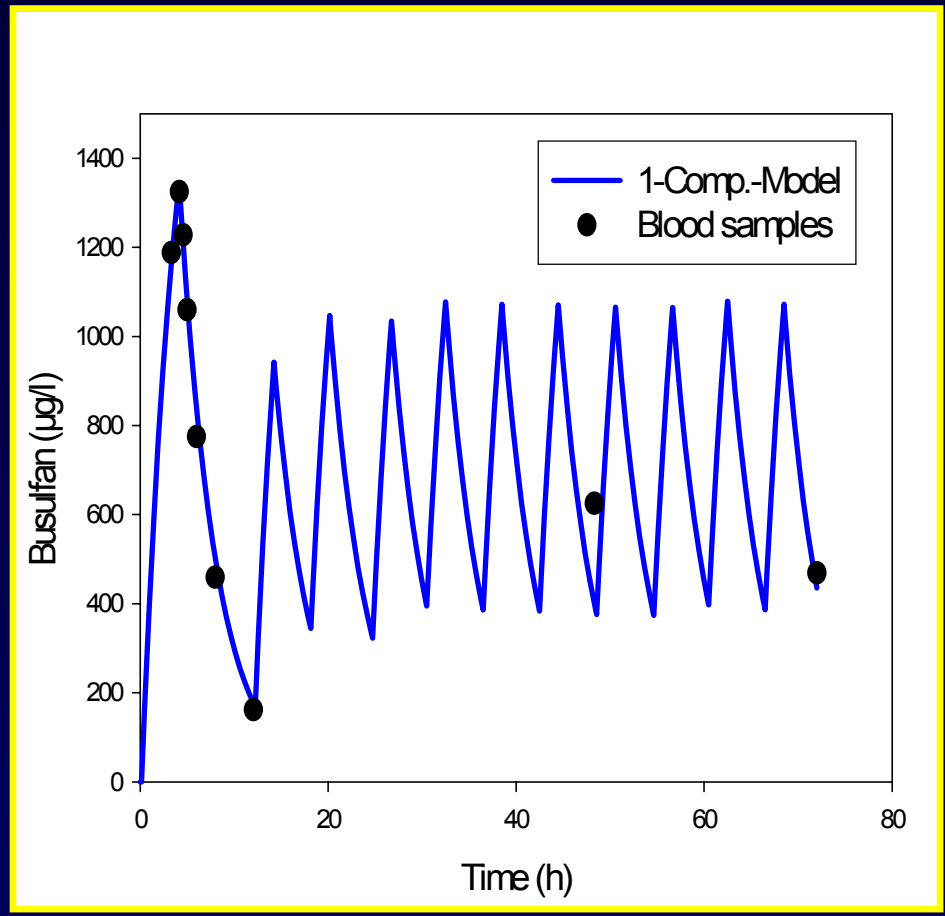
- Open, prospective pharmacological trial
- Multicenter study (4 sites)
- i.v. dose = 80% of the dose according to oral drug schedules

- 19 Patients (March 01 - Sept. 02)
- Median age : 4.0 years (0.9 - 17.3)
- Dosing: 0.8 mg/kg (n=12), 1 mg/kg (n=5), 30 mg/m^2 (n=2)
- 204 plasma samples, analysed by LC-MS

Results (19 patients)

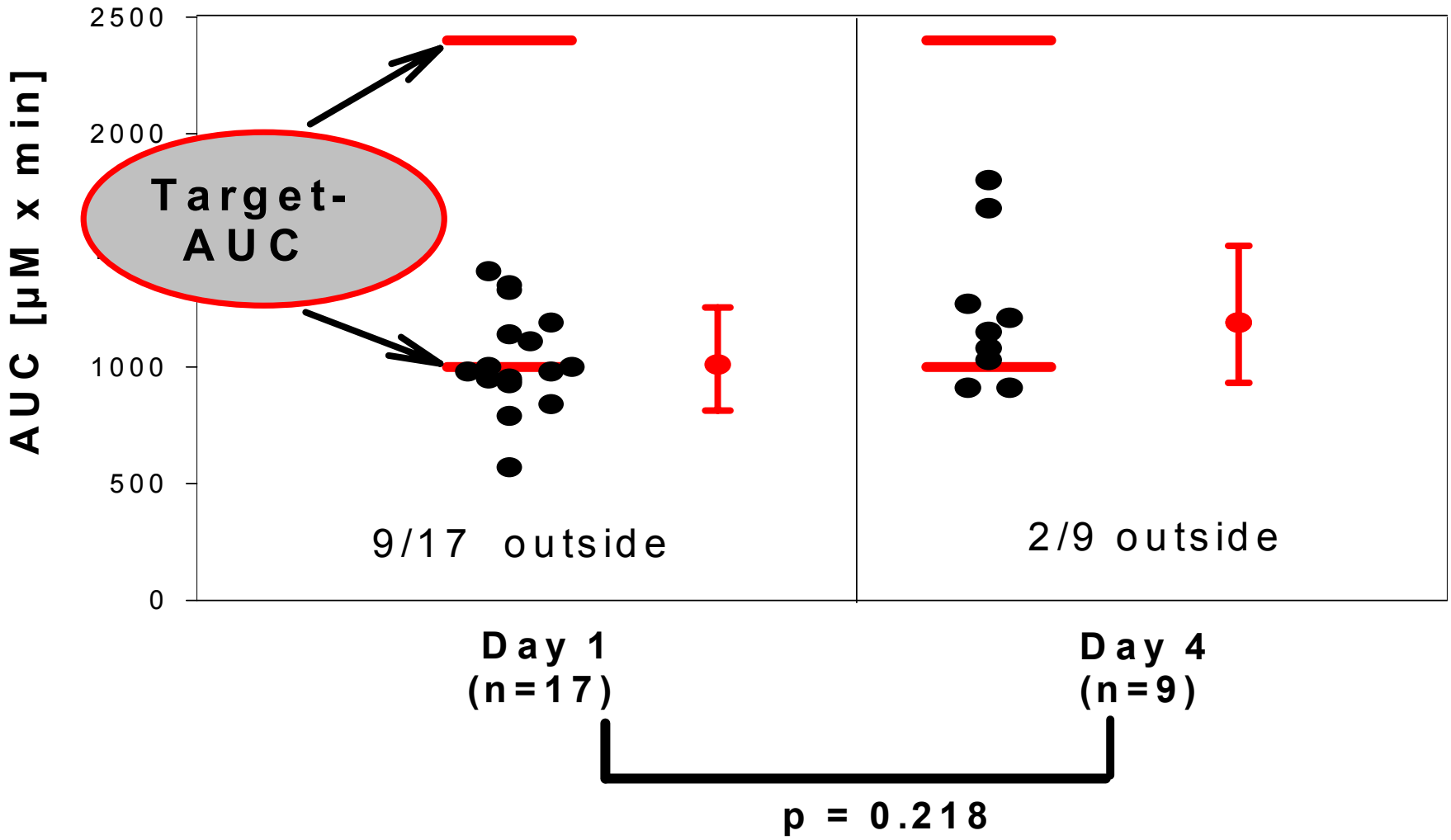


Busulfan plasma samples (n=205)



Individual fitting and measured busulfan conc. (Patient 1)

Area under Curve after i.v. Busulfan



Toxicities & Adverse events (Day+100 after BMT)

- Mucositis, nausea, vomiting, GvHD, elevated creatinine and transaminases
- 1 self-limiting tonic-clonic seizure (21 h after the end of the last busulfan i.v.-dose)
- Patient 1: died on day +61 post transplantation after gram-negative sepsis
- Patient 10: sudden agitation, ataxia, psychotic behaviour under i.v. busulfan
- No case of severe VOD

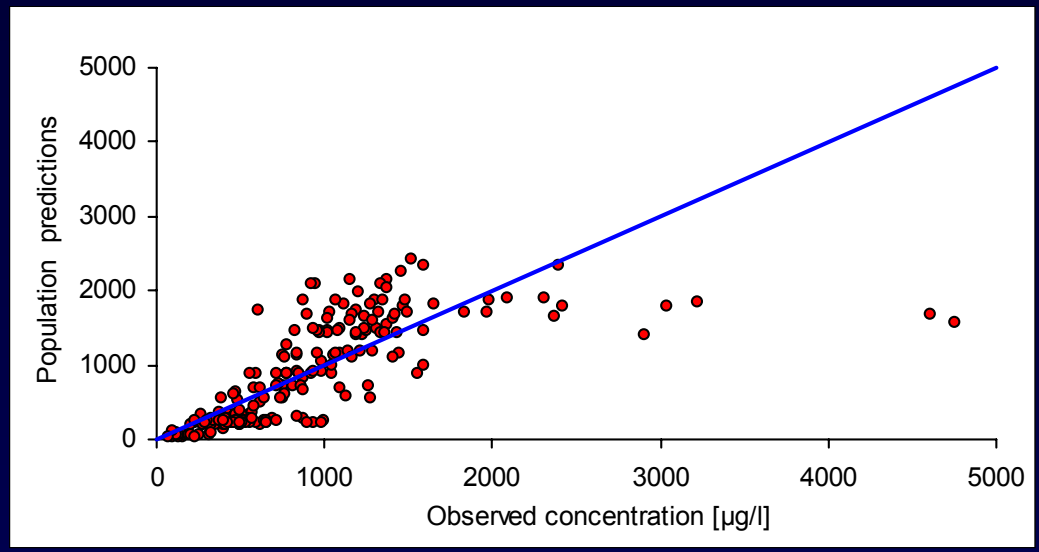
Population Analysis of i.v. Busulfan

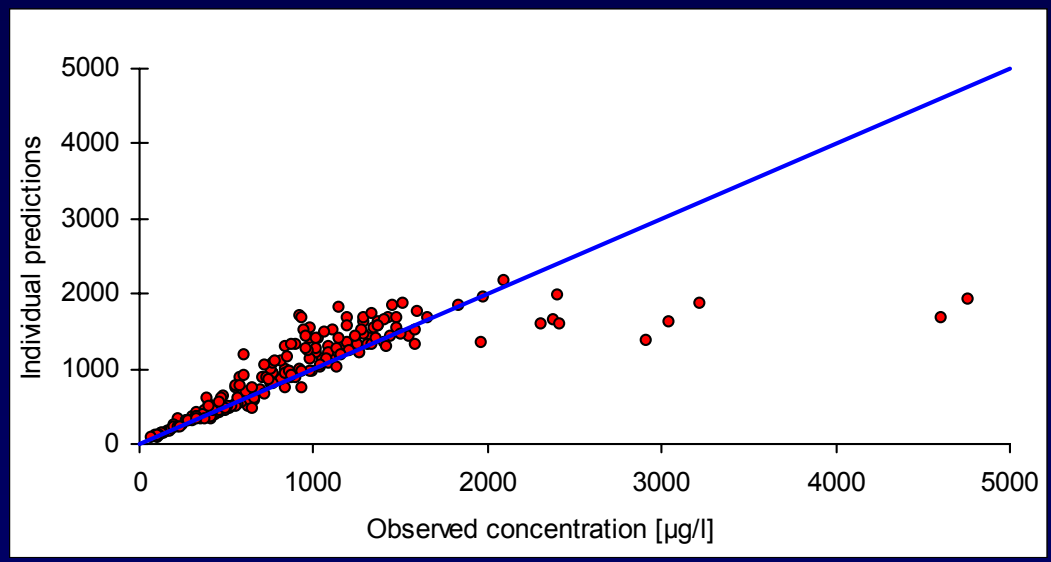
- NONMEM V, FOCE, 1-compartment model
- Proportional model for residual error and IOV
- proportional model for interindividual variability (IIV)

Run	OF	Covariates	IOV %	Cl (l/h)	IIVCl %	V (l)	IIVV %	Residual error
10	2527	BSA: Cl, V	---	4.74 (6)	20 (39)	12.2 (16)	30 (52)	39%
23	2513	BSA: Cl, V	Cl: 11% (20)	4.51 (7)	16 (52)	8.03 (21)	69 (54)	37%
17	2635	AGE/10: Cl, V	---	7.8 (13)	43 (24)	20 (14)	19 (63)	51%
15	2517	WEIGHT/70:Cl, V	---	13 (7)	21 (49)	36.2 (14)	21 (56)	39%
19	**2503**	**WEIGHT/20: Cl, V**	**Cl: 11.1% (28)**	**12.9 (18)**	**20 (144)**	**26.6 (80)**	**49 (300)**	**35%**
20	2511	WEIGHT/20: Cl, V	V: 23% (88)	13.2 (15)	21 (112)	27.3 (118)	53 (492)	37%
21	2503	WEIGHT/20: Cl, V	Cl: 11% (24.3) V: 3.8% (267)	12.9 (18)	20 (145)	26.6 (80)	49 (304)	35%

numbers in brackets are standard errors %

Population Analysis of i.v. Busulfan
- goodness of fit plots -





Population Analysis of i.v. Busulfan
- Results -

	Population Mean	Interindividual Variability	Intraindividual Variability
Cl (l/h/kg)	0,18	20%	11%
V (l/kg)	0,38	49%	---

- lower variability in AUC mainly due to high variability in absorption after oral administration
- weight slightly better than body surface area as a predictor of Cl and V
- interindividual variability in Cl higher than intraindividual variability

Population Analysis of oral and i.v. Busulfan

- 66 pts., 707 plasma samples
- starting point: best model for oral data:
  - One-compartment model
  - BSA on Cl, V
  - IIV for Cl, V, ka
  - IOV on Cl, V

Population Analysis of oral and i.v. Busulfan

	Population Mean	Interind. Variability	Intraind. Variability
Cl (l/h/kg)	0.162	29%	13%
V (l/kg)	0.516	24%	10%
ka (1/h)	0.566	109%	
F	98%		
res. error oral1	23% / 57 µg/l		
res. error oral2	34% / 87 µg/l		
res. error i.v.	29% / 74 µg/l		

- F much higher than expected
- weight slightly better than BSA as a covariate for Cl and V
- estimate of ka lower than without i.v. data
- estimate for IIV and IOV similar to oral data

Conclusion

- i.v. Busulfan displays a smaller interpatient variability in AUC compared to oral Busulfan (CV of 16% vs. CV of 37%)
- weight slightly better predictor for Cl and V than BSA
- Bioavailability higher than expected
  - dose of i.v. busulfan can be escalated
- dose individualisation based on plasma concentration measurements might be useful
- no age dependency found
  - possibly due to the low number of infants