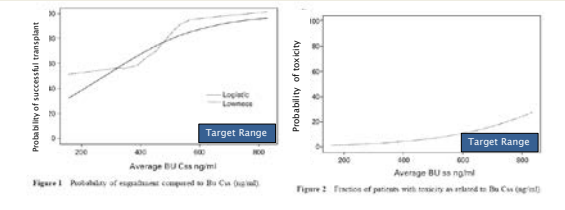
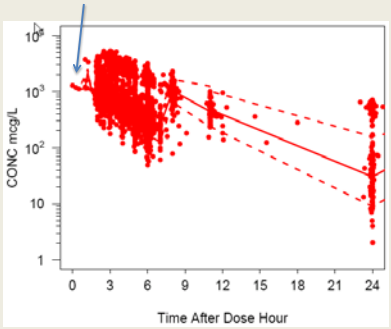
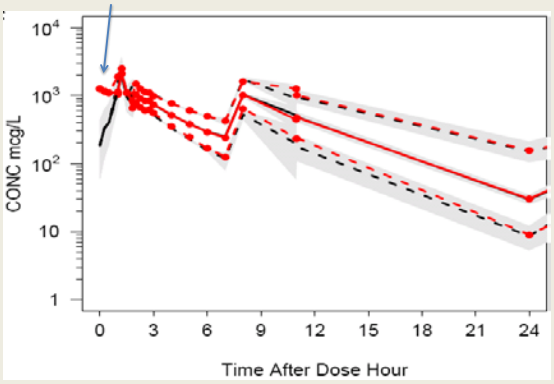
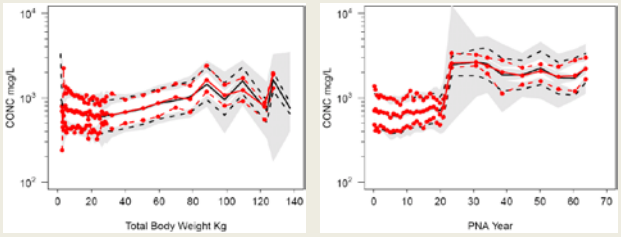
Slide 1	# Busulfan pharmacokinetics in neonates, infants, children and adults Nick Holford (1), Jeannine McCune (2,4,5), Jeff Barrett (3), Meagan Bemer (4), Jessica Tay (2), Scott Baker (4, 5), Alan Gamis (6) (1) Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand (2) University of Washington Schools of Pharmacy and Medicine, Seattle, WA (3) Children's Hospital of Philadelphia, Philadelphia, PA (4) Fred Hutchinson Cancer Research Center, Seattle, WA (5) Seattle Children's Hospital, Seattle, WA (6) Children's Oncology Group and Children's Mercy Hospital and Clinics, Kansas City, MO	Presented at PAGANZ 2013, University of Queensland, Brisbane, Australia on Feb 15 2013. http://www.paganz.org/wp-content/uploads/2013/03/PAGANZ_2013_busulfan_integrated_PK.pdf
Slide 2	 ## Busulphan Pharmacodynamics  Target Range 0.6 to 0.9 mg/L; Target Concentration 0.77 mg/L Corresponds to Target AUC of 1125 umoL*min q6h dosing Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30.	Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30.
Slide 3	 ## The Data Handful of Concs before end of infusion • Routinely collected busulfan concentration profiles were obtained at a national center for measuring busulfan concentrations • Dosing and demographic data was matched with 12,380 concentrations in 1610 patients • 92% of patients were under the age of 20  	

Slide 4	 **Pharmacokinetics** • Zero order input using dose and input duration recorded by clinical staff • Two compartment distribution • First order elimination • Between subject and between occasion variability estimated with exponential model for random effect • Combined additive and proportional residual error	
Slide 5	 **The Problem** • Clinical tradition has been to record 'dosing weight' (DWT) which is then used to predict the dose on a mg/kg basis • There are many 'dosing weight' formulas but the formula was not recorded and actual body weight was not known • 133 patients (108 adults and 25 children) had actual body weight (AWT) recorded	It is hoped that future studies of busulfan will record actual weight and use actual weight to predict doses using normal fat mass (see below).
Slide 6	 **A Solution...** $TBW_i = DWT \times FFEM_{DW} \times \exp(\eta_{DW})$ TBW=Total body weight prediction DWT=Dosing weight covariate $FFEM_{DW}$=Factor in women relative to men that predicts TBW	No systematic difference between TBW and DWT was found in males. Females had a slightly higher TBW.

Slide 7	**Size and Maturation** • Body Size – Fat mass was accounted for by using total body weight and fat free mass to predict normal fat mass – Theory based allometry was used to determine the best body size metric • Maturation – Maturation of clearance was described using a sigmoid Emax maturation model	Details of calculation of body size and maturation can be found in Holford N 2010. Dosing in children. Clin Pharmacol Ther 87(3):367-370.
Slide 8	**Evaluation** Handful of Concs before end of infusion  	The VPC shows excellent predictions of observed concentrations except samples taken before the end of the (usually) 2 hour infusion. It is probable that these samples were contaminated because there were drawn from the same catheter used to infuse busulfan without adequate flushing.
Slide 9	**Evaluation of Covariates**  	The two main covariates, weight and age, show no residual mis-specification of the model. The higher concentrations in adults reflect the use of daily rather than 6 h dosing with samples drawn mainly in the first 6 hours after the dose.

Slide 10

Structural Parameters

Parameter	Description	Units	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
CL	Clearance	L/h/70kg	12.5	1.1%	12.2	12.7
V1	Central volume of distribution	L/70kg	15.8	6.6%	13.5	17.9
Q	Inter-compartmental clearance	L/h/70kg	148.1	7.2%	126.4	168.0
V2	Peripheral volume of distribution	L/70kg	33.9	3.0%	32.1	35.8
$FFAT_{CL}$	Fat fraction for clearance (from ABW data)	.	0.509	42.8%	0.110	0.950
$FFAT_{V}$	Fat fraction for volume (from ABW data)	.	0.203	51.6%	0.016	0.429
$TM50_{CL}$	PMA at 50% maturation	weeks	45.7	4.3%	41.6	49.2
$HILL_{CL}$	Hill coefficient for maturation	.	2.3	9.7%	1.93	2.74
$FFEM_{V}$	Fractional difference in total volume (V1+V2) in females		1.07	1.2%	1.05	1.10
$FFEM_{DW}$	Fractional difference in dosing weight in females		1.08	1.7%	1.05	1.11

Both clearance and volume were better related to normal fat mass than either predicted total body weight or fat free mass. Maturation of busulfan clearance reaches 50% of the predicted size standardized adult value around 6 weeks after full term (40 weeks) gestation.
There is a slightly larger steady state volume of distribution in females. Predicted total body weight also tended to be slightly larger than dosing weight in females.

Slide 11

Test of Allometric Theory

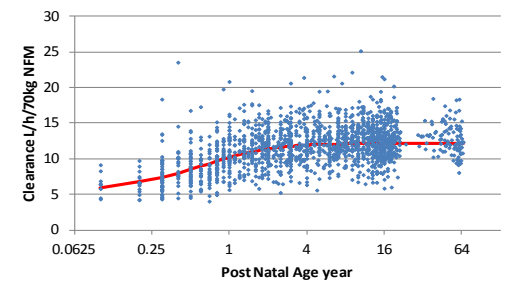
- Wide range (95% interval) of weight (5-90 kg) and large sample size (N=1610)
- Allometric exponents estimated with starting value of 0.67 for CL and Q and 1.25 for V1 and V2
- Non-parametric bootstrap used to estimate average and 95% confidence interval for allometric exponents

Parameter	Description	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
PWR_CL	Allometric exponent for CL	0.767	3.1%	0.724	0.817
PWR_V1	Allometric exponent for V1	1.059	9.1%	0.932	1.321
PWR_Q	Allometric exponent for Q	0.845	11.8%	0.695	1.065
PWR_V2	Allometric exponent for V2	0.993	4.0%	0.888	1.060

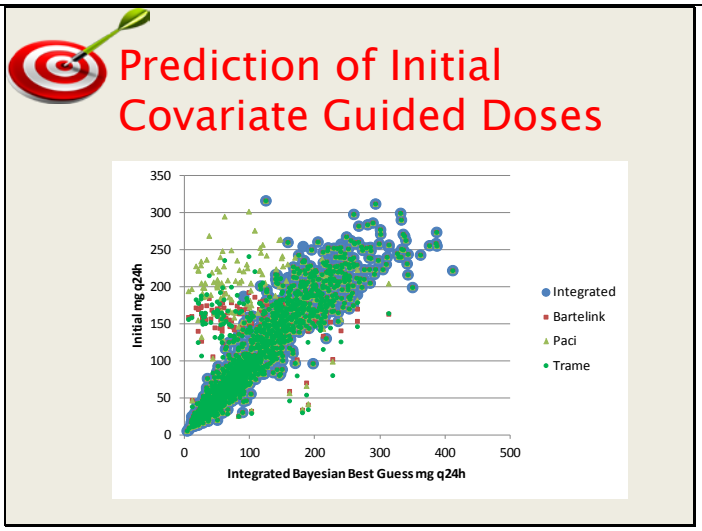
Wide range (95% interval) of weight (5-90 kg) and large sample size (N=1610) provides a design suitable for testing the predictions of theory based allometry. The 95% confidence interval of the estimate of the exponent for clearance is narrow and includes the theoretical value of ¾. Similar agreement between theory and observation is seen for V1 and V2 (theoretical value of 1). It is uncertain if intercompartmental clearance is more like elimination clearance or volume of distribution. The confidence interval is relatively wide and includes both ¾ and 1. There is no support for an allometric exponent of 2/3 for clearance which would be expected if body surface area was an appropriate size metric.

Slide 12

Prediction of Maturation



The maturation of size standardized clearance shows about a 2 fold range from premature neonates to adults. There is clearly substantial unexplained between and within subject variability even after accounting for age and weight. The unpredictable, apparently random, between subject variability can be reduced by using target concentration intervention to improve individual estimates of clearance. This in turn can be used to predict the busulfan dosing regimen to achieve the target concentration.

Slide 13		The integrated model developed from PK data from children and adults was used to obtain a Bayesian estimate of clearance for each patient. This estimate of clearance was used to make the best guess estimate of the daily dose required to reach a target steady state concentration of 0.77 mg/L. Initial dose predictions were made using just covariate based models for clearance according to the current integrated study and those reported in the literature (Bartelink 2012, Paci 2012, Trame 2011). In general all methods gave reasonable predictions of the required daily dose except when the non-integrated methods were applied in children (best guess doses less than 150 mg/day). There was one instance where the integrated model initial dose was just over twice as big as the required daily dose. Bartelink IH, Boelens JJ, Bredius RGM, Egberts ACG, Wang C, Bierings MB, Shaw PJ, Nath CE, Hempel G, Zwaveling J, Danhof M, Knibbe CAJ 2012. Body Weight-Dependent Pharmacokinetics of Busulfan in Paediatric Haematopoietic Stem Cell Transplantation Patients: Towards Individualized Dosing. Clin Pharmacokinet 51(5):331-345. Paci A, Vassal G, Moshous D, Dalle JH, Bleyzac N, Neven B, Galambrun C, Kemmel V, Abdi ZD, Broutin S, Petain A, Nguyen L 2012. Pharmacokinetic behavior and appraisal of intravenous busulfan dosing in infants and older children: the results of a population pharmacokinetic study from a large pediatric cohort undergoing hematopoietic stem-cell transplantation. Ther Drug Monit 34(2):198-208. Trame MN, Bergstrand M, Karlsson MO, Boos J, Hempel G 2011. Population pharmacokinetics of busulfan in children: increased evidence for body surface area and allometric body weight dosing of busulfan in children. Clin Cancer Res 17(21):6867-6877.

Slide 14

Conclusion

- Theory based allometry confirmed experimentally for CL, V1, (Q) and V2
- Normal fat mass describes allometric size better than other methods
- Maturation of busulfan clearance reaches half of adult values around 6 weeks after full term delivery
- Initial doses of busulfan can be predicted from infants to adults using the same method

Slide 15

Random Effect Parameters

Parameter	Description	Bootstrap Estimate	Bootstrap RSE	2.5% ile	97.5% ile
FDW	BSV in Fraction of Dosing Weight	0.166	7.8%	0.134	0.185
CL	BSV in clearance	0.215	4.7%	0.195	0.234
V1	BSV in central volume	0.410	10.8%	0.329	0.506
Q	BSV in intercompartmental clearance	0.922	9.1%	0.730	1.059
V2	BSV in peripheral volume	0.120	23.8%	0.059	0.183
CL	BOV in clearance	0.113	14.8%	0.081	0.145
V1	BOV in central volume	0.244	20.0%	0.147	0.327
Q	BOV in intercompartmental clearance	0.577	24.6%	0.330	0.903
V2	BOV in peripheral volume	0.212	12.4%	0.162	0.264
RUV_{ADD}	Additive RUV (mcg/L)	26.2	13.7%	18.9	32.8
RUV_{PROP}	Proportional RUV	0.0387	12.8%	0.0298	0.0468

BSV = Between subject variability (sqrt(OMEGA))
BSV = Between occasion variability (sqrt(OMEGA))
RUV= Residual unidentified variability (sqrt(SIGMA))

The between occasion variability in clearance is an estimate of the irreducible within subject variation in clearance from which cannot be improved by target concentration intervention.

Slide 16

Demographics

Statistic	Units	average	2.5% ile	97.5% ile
PNA	year	9.8	0.3	58.4
PMAW	week	551	56	3089
AWT	kg	30.8	5.2	89.7
DWT	kg	30.2	5.2	84.4
FFMKG	kg	23.3	4.3	64.5
HTCM	cm	116	58	181
BMI	kg/m^2	18.9	12.6	30.8
IBW	kg	14.9	-38.3	76.1

The percentile are derived from the empirical distribution of baseline values for these demographic features.
Note that ideal body weight (IBW) is frequently negative in children because the empirical IBW formula was developed in adults and is not appropriate for children.