Characterisation of the clinical pharmacokinetics of actinomycin D and the influence of ABCB1 pharmacogenetic variation on actinomycin D disposition in children with cancer

Christopher R. Hill, Michael Cole, Julie Errington, Ghada Malik, Alan V. Boddy and Gareth J. Veal

Supplementary Material

Supplementary Table S1. Summary of pharmacokinetic data from 117 patients receiving Actinomycin D

Sample time	No. of patients	Act D plasma concentration (µg/L)			CV (%)
		Median	Minimum	Maximum	
5 min	13	128	64.7	186	27.9
15 min	101	24.4	5.3	122	73.2
30 min	113	9.8	3.3	40.7	57.0
1 h	16	6.3	3.3	38.1	95.9
2 h	108	4.8	1.4	24.8	52.4
4 h	103	3.7	1.3	16.1	54.9
6 h	38	3.2	1.2	9.1	53.9
8 h	35	2.8	1.2	6.6	41.6
22h	12	1.8	1.1	4	42.6
24h	73	1.8	0.7	4.8	45.1
26h	38	1.9	0.7	4.3	43.0

Abbreviations: Act D, actinomycin D; CV, coefficients of variation.

Supplementary Table S2. Comparison of population pharmacokinetic models 1 and 2.

Parameter	Model 1	Model 2
CL (L/h/70kg)	11.9	13.9
Q2 (L/h/70kg)	8.1	15.3
Q3 (L/h/70kg)	22.4	36.2
V1 (L/70kg)	3.9	7.5
V2 (L/70kg)	11	17.1
V3 (L/70kg)	334	388
Inter individual variation (IIV)		
CL (%CV)	42.9	28.3
V1 (%CV)	52.6	28.5
Q3 (%CV)	-	34.9
V3 (%CV)	-	41.1
Correlation		
CL ~ V1	-0.34	-
CL ~ Q3	-	0.78
CL ~ V3	-	0.75
Q3 ~ V3	-	0.61
Residual %CV	23.2	18.5
Number of parameters	10	14
OFV	1573	1372

Abbreviations: CL, clearance; Q2 and Q3, inter-compartmental clearance values for compartments 2 and 3; V1, central volume of distribution; V2 and V3, volume of distribution of the second and third compartments; CV, coefficients of variation; OFV, objective function value.

Supplementary Table S3. Summary of toxicity data following Actinomycin D treatment (n=146)

Toxicity	No. of patients (%)	
	All CTC grades	Grades (3/4)
Granulocytes	63 (44)	50 (35)
Leucocytes	60 (42)	37 (26)
Haemoglobin	57 (39)	23 (16)
Infection	22 (15)	19 (13)
Platelets	28 (20)	13 (9)
Fever	22 (15)	15 (10)
ALT	11 (8)	2 (1)
Neuroconstipation	6 (4)	0
Neuromotor	5 (4)	0
AST	3 (4)	1 (1)
Neurosensory	3 (2)	1 (1)
Bilirubin	3 (2)	0
Neurocorticol	1 (1)	1 (1)
Hepatic enlargement	0	0
Ascites	0	0
Haemorrhage	0	0

Note: Toxicity grades based on National Cancer Institute Common Toxicity Criteria (version 3.0)

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CTC, Common Toxicity Criteria

Supplementary Table S4. Genotype and allelic frequencies for the studied ABCB1 polymorphisms

ABCB1 polymorphism	No. of patients with genotype (frequencies)			Allelic frequencies‡	
	Allele†	Heterozygous	Allele 2†	p	q
1236 C>T	47 (0.34)	64 (0.46)	29 (0.21)	0.56	0.44
2677G>T/A	36 (0.26)	GT – 66 (0.47) GA – 9 (0.06) TA – 3 (0.02)	26 (0.19)	0.53	0.43
3435C>T	32 (0.23)	69 (0.49)	39 (0.28)	0.48	0.53

†Allele 1- homozygous for allele 1, Allele 2 – homozygous for allele 2

‡Hardy-Weinberg notation for allele frequencies (p, frequency for allele 1; q, frequency for allele 2)

Supplementary Table S5. Effect of ABCB1 polymorphisms on Actinomycin D clearance

ABCB1 Polymorphism	Mean Act D Clearance L/h (L/h/m^2)			Significance‡
	Allele 1†	Heterozygous	Allele 2†	
1236C>T	5.8 (6.7)	5.7 (6.5)	5.8 (6.4)	0.99 (0.87)
2677G>T/A	6.1 (7.0)	5.7 (6.6) GA – 5.5 (5.1) TA – 5.2 (2.7)	5.9 (6.3)	0.92 (0.5)
3435C>T	6.1 (6.6)	5.5 (6.7)	6.1 (6.2)	0.77 (0.68)

†Allele 1- homozygous for allele 1, Allele 2 – homozygous for allele 2

‡Statistical analysis performed was the one-way ANOVA. One test was performed per genotype, assessing global significance between genotype and CL-FSA. $p<0.002$ accepted as significant.