Supplementary materials

Predicting Volume of Distribution in Neonates: Performance of Physiologically Based Pharmacokinetic Modelling

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Supplementary figures

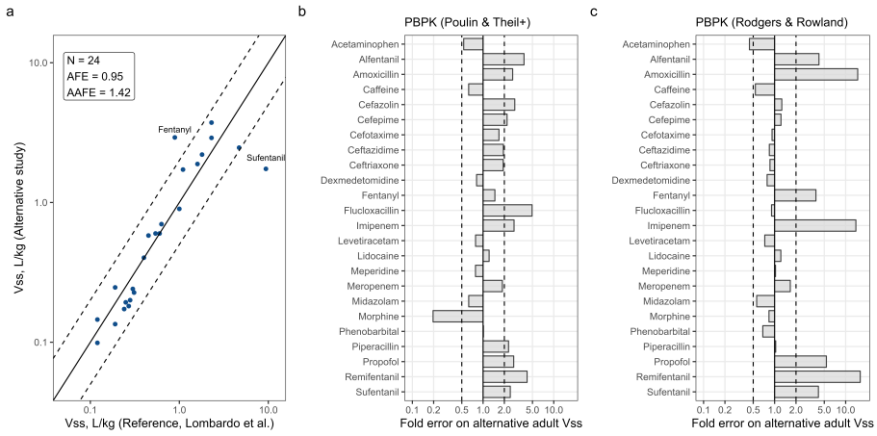

Figure S1. Comparison of alternative volumes of distribution at steady state (Vss) in adults with original reference data (panel **a**) and the accuracy of two physiologically based pharmacokinetic modelling (PBPK) methods in predicting Vss when the alternative Vss is used as comparator (panels **b** and **c**). PBPK predictions are done with either the Poulin & Theil with Berezhkovskiy correction method (panel **b**) or with the Rodgers & Rowland method (panel **c**). Dashed lines denote a twofold interval around the line of unity (solid line). N: number of drugs, AFE: average fold error, AAFE: absolute average fold error.

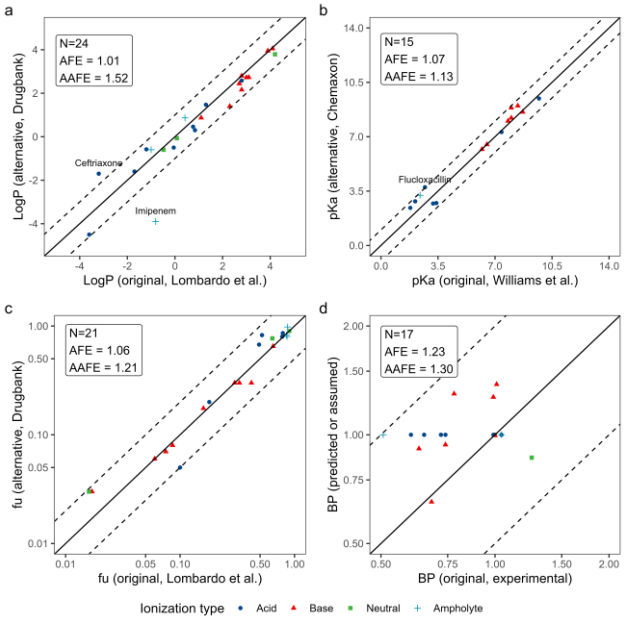

Figure S2. Comparison between original input parameter values (x-axes) and alternative input values (y-axes) of the physiologically based pharmacokinetic (PBPK) models. Input parameters evaluated are LogP (panel **a**), pKa of the strongest acid or base (panel **b**), free fraction in plasma (fu, panel **c**) and the blood-to-plasma ratio (BP, panel **d**). Original values originated from the Lombardo et al. database (1)(LogP and fu), the Williams et al. database (pKa) (2) or a variety of sources (BP). Alternative values were sourced from Drugbank (LogP and fu), predicted with the Chemaxon method (pKa) or predicted using the Simcyp software (BP, only for bases and neutrals, for acids: assumed to be equal to 1). The solid lines denote the line of unity, the dashed lines denote a log unit difference (panels **a** and **b**) or a twofold difference (panels **c** and **d**). N: number of drugs with full data, AFE: average fold error, AAFE: absolute average fold error.

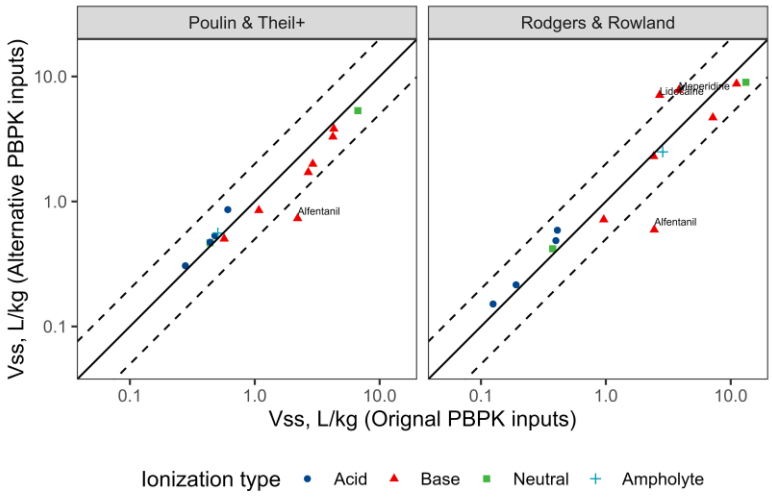

Figure S3. Comparison between physiologically based pharmacokinetic (PBPK) predicted volume of distributions at steady state (Vss) in adults when either the original parameters or alternative input parameters are used. PBPK predictions are done with either the Poulin & Theil with Berezhkovskiy correction method (**left** panel) or with the Rodgers & Rowland method (**right** panel). Input parameter values can be found in Table 1 (original inputs) or supplementary Table 2 (alternative inputs). The solid line denotes the line of unity, while the dashed lines denote a twofold interval around the line of unity.

Supplementary tables

Table S1: Reference- and alternative volumes of distribution at steady state (Vss) in adults

Drug	Reference Vss (L/kg) (1)	Alternative Vss (L/kg)	Source alternative Vss	Fold error (alt/ref)
Acetaminophen	1.00	0.90	(3)	0.90
Alfentanil	0.45	0.58	(4)	1.29
Amoxicillin	0.25	0.19	(5)	0.77
Caffeine	0.63	0.70	(6)	1.11
Cefazolin	0.12	0.10	(7)	0.82
Cefepime	0.28	0.20	(8)	0.71
Cefotaxime	0.19	0.25	(9)	1.30
Ceftazidime	0.31	0.23	(9)	0.73
Ceftriaxone	0.12	0.15	(10)	1.21
Dexmedetomidine	1.60	1.89	(11)	1.18
Fentanyl	0.89	2.92	(12)	3.28
Flucloxacillin	0.19	0.13	(13)	0.71
Imipenem	0.24	0.17	(14)	0.72
Levetiracetam	0.60	0.60	(15)	1.00
Lidocaine	1.80	2.20	(16)	1.22
Meperidine	2.30	3.73	(17)	1.62
Meropenem	0.30	0.24	(18)	0.80
Midazolam	1.10	1.72	(19)	1.56
Morphine	2.30	2.90	(20)	1.26
Phenobarbital	0.54	0.60	(21)	1.11
Piperacillin	0.27	0.18	(22)	0.67
Propofol	4.70	2.47	(23)	0.53
Remifentanil	0.40	0.40	(24)	1.01
Sufentanil	9.40	1.74	(25)	0.19

Table S2: Alternative input values for physiologically based pharmacokinetic (PBPK) models

Drug	LogP (Drugbank)	pka1 (Chemaxon)	fu (Drugbank)	BP (predicted [a] or assumed [b])
Acetaminophen	0.46	9.46	0.825	1.00 [b]
Alfentanil	2.16	6.50	0.080	0.92 [a]
Amoxicillin	0.87	3.23	0.830	1.00[b]
Caffeine	-0.07	neutral	0.770	1.00 [b]
Cefazolin	-0.58	2.84	0.200	1.00 [b]
Cefepime	-4.50	/	0.800	1.00 [b]
Cefotaxime	-0.50	2.73	NA	/
Ceftazidime	-1.60	2.42	0.861	1.00 [b]
Ceftriaxone	-1.70	2.70	0.050	/
Dexmedetomidine	2.80	/	0.060	/
Fentanyl	4.05	8.99	0.175	1.27 [a]
Flucloxacillin	2.58	3.75	NA	/
Imipenem	-3.90	/	0.800	/
Levetiracetam	-0.60	16.09	0.900	/
Lidocaine	2.44	8.01	0.300	1.30 [a]
Meperidine	2.72	8.59	0.300	1.38 [a]
Meropenem	-0.60	/	0.980	1.00 [b]
Midazolam	2.73	6.19	0.030	0.65 [a]
Morphine	0.87	8.21	0.650	1.00 [a]
Phenobarbital	1.47	7.30	0.675	1.00 [b]
Piperacillin	0.30	/	NA	1.00 [b]
Propofol	3.79	neutral	0.030	0.86 [a]
Remifentanil	1.40	/	0.300	/
Sufentanil	3.95	8.86	0.070	0.94 [a]

[a] : predicted by Simcyp V22 from physicochemical data (bases)
[b]: assumed to be equal to 1.00 (acids)
/: not applicable, as original data already used this source
BP: blood to plasma ratio, fu: free fraction in plasma, NA: not available, pKa1: pKa of strongest acid or base (acid in case of ampholyte).

Table S3: Studies describing the volume of distribution at steady state (Vss) in neonates

Drug	Study or sub-study	N	females	Postnatal age (days), range	Gestational age (weeks), range	Body weight (kg), mean	Preterms	Reported Vss (L/kg)
Acetaminophen	van Ganzewinkel et al. (2014)(26)	15	47%	0 - 7	24 - 32	1.21	100%	0.76
Acetaminophen	Cook et al. (2016) (27)	35	50%*	1 - 26	23 - 41	2.06	49%	1.07
Alfentanil	Killian et al. (1990) (28) (PT)	5	50%*	0 - 3	26 - 36	NA	100%	0.84
Alfentanil	Killian et al. (1990) (28) (T)	5	50%*	0 - 3	36 - 38	NA	0%	0.82
Alfentanil	Pokela et al. (1992) (29)	15	50%*	0 - 2	30 - 40	2.50	50%*	0.53
Amoxicillin	Huisman-de Boer et al. (1995) (30)	17	35%	3 - 3	25 - 36	1.18	100%	0.67
Amoxicillin	Charles et al. (1997) (31)	40	50%*	1 - 3	24 - 32	1.12	100%	0.60
Amoxicillin	Pullen et al. (2006) (32)	150	48%	0 - 9	25 - 42	2.29	50%*	0.65
Amoxicillin	Pullen et al. (2007) (33)	32	25%	10 - 52	26 - 41	2.27	50%*	0.66
Amoxicillin	Bijleveld et al. (2018) (34)	125	41%	2 - 5	36 - 42	3.34	0%	0.69
Amoxicillin	Tang et al. (2019) (35)	187	50%*	1 - 37	28 - 41	2.99	50%*	1.21
Caffeine	Charles et al. (2008) (36)	110	53%	1 - 45	24 - 29	0.99	100%	0.85
Cefazolin	Deguchi et al. (1988) (37) (T)	3	33%	5 - 7	39 - 40	3.36	0%	0.23
Cefazolin	Deguchi et al. (1988) (37) (PT)	8	25%	2 - 28	30 - 35	1.85	100%	0.30
Cefazolin	De Cock et al. (2014) (38)	36	50%*	1 - 30	24 - 40	2.76	50%*	0.31
Cefepime	Lima-Rogel et al. (2008) (39)	31	52%	6 - 58	27 - 38	1.40	50%*	0.41
Cefepime	Shoji et al. (2016) (40) (T)	12	50%*	1 - 30	36 - 42	NA	0%	0.35
Cefepime	Shoji et al. (2016) (40) (PT)	32	50%*	1 - 30	22 - 36	NA	100%	0.40
Cefepime	Zhao et al. (2020) (41)	85	50%*	1 - 25	28 - 42	3.21	50%*	0.62
Cefotaxime	Kearns et al. (1989) (42)	18	28%	1 - 7	24 - 32	1.02	100%	0.46
Cefotaxime	Aujard et al. (1989) (43) (PT)	10	50%*	0 - 7	28 - 36	NA	100%	0.38
Cefotaxime	Aujard et al. (1989) (43) (T)	6	50%*	0 - 7	37 - NA	NA	0%	0.45
Cefotaxime	Shang et al. (2022) (44)	51	39%	1 - 3	30 - 41	2.31	12%	0.38
Ceftazidime	Van Den Anker et al. (1995) (45)a	10	50%*	3 - 3	37 - NA	3.06	0%	0.34
Ceftazidime	Van Den Anker et al. (1995) (45)b	9	50%*	3 - 3	37 - NA	3.37	0%	0.34
Ceftazidime	Van Den Anker et al. (1995) (46)	136	50%*	3 - 3	24 - 37	1.41	100%	0.35
Ceftazidime	Van Den Anker et al. (1995) (47)c	13	50%*	3 - 3	26 - 32	1.17	100%	0.32
Ceftazidime	Van Den Anker et al. (1995) (47)d	25	50%*	3 - 3	26 - 32	1.14	100%	0.30
Ceftazidime	Van Den Anker et al. (1995) (48)e	11	50%*	3 - 3	25 - 32	1.15	100%	0.36
Ceftazidime	Van Den Anker et al. (1995) (48)e	11	50%*	10 - 10	25 - 32	1.15	100%	0.29
Ceftazidime	Van Den Anker et al. (1995) (48)f	12	50%*	3 - 3	27 - 32	1.02	100%	0.33
Ceftazidime	Van Den Anker et al. (1995) (48)f	12	50%*	10 - 10	27 - 32	1.02	100%	0.32
Ceftazidime	Wang et al. (2018) (49)	43	50%*	1 - 60	27 - 41	2.73	50%*	0.67
Ceftriaxone	McCracken et al. (1983) (50)	26	50%*	1 - 45	NA - NA	1.83	50%*	0.55
Ceftriaxone	Martin et al. (1984) (51)	12	50%*	1 - 30	NA - NA	2.88	50%*	0.52
Ceftriaxone	Schaad et al. (1985) (52) (T)	6	33%	1 - 7	37 - 41	3.38	0%	0.32
Ceftriaxone	Schaad et al. (1985) (52) (PT)	10	30%	1 - 8	34 - 36	2.36	100%	0.43
Ceftriaxone	Mulhall et al. (1985) (53)g	12	50%*	1 - 16	26 - 41	1.88	50%*	0.33
Ceftriaxone	Mulhall et al. (1985) (53)h	10	50%*	1 - 16	26 - 41	1.88	50%*	0.39
Dexmedetomidine	Chrysostomou et al. (2014) (54)	18	61%	0 - 18	28 - 36	1.70	100%	2.70
Dexmedetomidine	McAdams et al. (2020) (55)	7	50%*	0 - 5	37 - 41	3.51	0%	7.48
Fentanyl	Koehntop et al. (1986) (56)	14	50%*	0 - 14	NA - NA	2.90	50%*	5.10

Fentanyl	Gauntlett et al. (1988) (57)	11	50%*	1 - 59	36 - 40	2.80	0%	8.29
Flucloxacillin	Herngren et al. (1987) (58)	9	50%*	1 - 14	33 - 41	2.49	44%	0.28
Flucloxacillin	Pullen et al. (2006) (59)	55	50%*	0 - 44	26 - 42	1.39	50%*	0.54
Imipenem	Gruber et al. (1985) (60)	10	50%*	1 - 8	NA - NA	2.71	50%*	0.38
Imipenem	Freij et al. (1985) (61)	14	50%*	0 - 10	31 - 42	2.40	50%*	0.66
Imipenem	Reed et al. (1990) (62)	41	51%	1 - 6	22 - 36	1.19	100%	0.55
Imipenem	Yoshizawa et al. (2013) (63)	60	50%	0 - 34	30 - 41	2.93	50%*	0.47
Levetiracetam	Merhar et al. (2011) (64)	18	44%	0 - 32	35 - 41	3.50	50%*	0.89
Levetiracetam	Sharpe et al. (2012) (65)	18	50%	1 - 5	36 - 41	3.24	0%	1.01
Levetiracetam	Lima-Rogel et al. (2018) (66)	20	45%	3 - 25	28 - 40	2.90	30%	0.65
Lidocaine	van den Broek et al. (2011) (67)	46	33%	0 - 10	25 - 43	2.93	39%	2.96
Meperidine	Pokela et al. (1992) (68) (PT+T)	14	36%	0 - 54	32 - 41	3.46	50%*	6.52
Meperidine	Pokela et al. (1992) (68) (PT)	3	33%	1 - 23	28 - 33	1.90	100%	7.17
Meropenem	van den Anker et al. (2009) (69) (PT)	23	43%	0 - 28	29 - 36	1.87	100%	0.52
Meropenem	van den Anker et al. (2009) (69) (T)	15	33%	0 - 28	37 - 42	3.17	0%	0.31
Meropenem	Padari et al. (2012) (70)	19	37%	0 - 56	32 - NA	0.98	50%*	0.31
Meropenem	Lima-Rogel et al. (2021) (71)	40	53%	5 - 28	26 - 41	1.62	50%*	0.46
Midazolam	Jacqz-Aigrain et al. (1990) (72) (T)	7	50%*	2 - 5	37 - 41	3.34	0%	0.90
Midazolam	Jacqz-Aigrain et al. (1990) (72) (PT)	3	50%*	2 - 5	34 - 35	2.57	100%	0.98
Midazolam	Jacqz-Aigrain et al. (1992) (73)	15	50%*	1 - 5	29 - 41	2.30	27%	1.10
Midazolam	Harte et al. (1997) (74)	10	50%*	2 - 4	25 - 30	1.04	100%	1.15
Midazolam	Favié et al. (2019) (75)	118	40%	0 - 5	36 - NA	3.47	0%	1.55
Morphine	Chay et al. (1992) (76) (T)	7	37%	0 - 4	37 - 41	3.22	0%	2.07
Morphine	Chay et al. (1992) (76) (PT)	12	37%	0 - 4	28 - 36	2.19	100%	2.04
Morphine	Pokela et al. (1993) (77) (T)	16	50%*	0 - 57	38 - 42	3.85	0%	1.66
Morphine	Pokela et al. (1993) (77) (PT)	4	50%*	1 - 24	28 - 36	2.08	100%	1.35
Morphine	Farrington et al. (1993) (78) (T)	6	50%*	1 - 6	37 - 40	3.15	0%	6.47
Morphine	Farrington et al. (1993) (78) (PT)	5	50%*	1 - 6	32 - 36	2.34	100%	3.26
Morphine	Anand et al. (2008) (79)	875	50%*	0 - 3	23 - 32	1.04	100%	2.71
Phenobarbital	Heimann et al. (1977) (80)	14	50%*	0 - 28	NA - NA	NA	50%*	0.85
Phenobarbital	Grasela et al. (1985) (81)	59	41%	1 - 16	24 - 42	1.52	78%	0.96
Phenobarbital	Donn et al. (1985) (82)	10	50%*	0 - 6	37 - 41	3.06	0%	0.97
Phenobarbital	Sima et al. (2018) (83)	36	42%	2 - 7	37 - NA	3.19	0%	0.49
Phenobarbital	Favié et al. (2019) (75)	113	37%	2 - 5	36 - NA	3.38	0%	1.03
Phenobarbital	Pokorna et al. (2019) (84)	40	57%	0 - 1	36 - NA	3.26	0%	0.48
Piperacillin	Kacet et al. (1992) (85) (PT)	14	50%*	3 - 3	29 - 35	NA	100%	0.55
Piperacillin	Kacet et al. (1992) (85) (T)	4	50%*	3 - 3	38 - 40	NA	0%	0.54
Piperacillin	Li et al. (2013) (86)	71	50%*	1 - 56	26 - 41	2.76	50%*	0.37
Propofol	Allegaert et al. (2007) (87)	25	16%	1 - 25	26 - 40	2.93	40%	5.56
Propofol	Allegaert et al. (2007) (88) (T)	3	50%*	8 - 25	39 - 40	2.51	0%	3.37
Propofol	Allegaert et al. (2007) (88) (PT)	6	50%*	4 - 25	25 - 36	2.51	100%	4.29
Remifentanil	Ross et al. (2001) (89)	8	50%*	5 - 56	NA - NA	3.74	50%*	0.45
Sufentanil	Greeley et al. (1987) (90)	9	50%*	1 - 30	NA - NA	3.24	50%*	4.15
Sufentanil	Pokorna et al. (2021) (91)	12	75%	0 - 1	37 - 40	3.17	0%	11.8

Sub-study specification: [a]: asphyxiated, [b]: non-asphyxiated, [c]: once daily, [d]: twice daily, [e]: non exposed to indomethacin, [f]: exposed to indomethacin, [g]: single dose, [h]: multiple dose, (T): term, (PT): preterm.
*: assumed, no data available
N: number of neonates, NA: not available

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