Table 2
Kinetic disposition of lorazepam and its metabolite glucuronide in parturients treated with a single oral dose of 2 mg *rac*-lorazepam; mean (CI 95%)

	Lorazepam isomeric mixture	Lorazepam-glucuronide isomeric mixture
C_{max} (ng/ml)	12.96 (9.42–16.49)	35.55 (8.27–62.83)
t_{max} (h)	3.10 (2.57–3.63)	4.33 (2.90–5.77)
$t_{1/2a}$ (h)	3.16 (2.62–3.68)	1.37 (1.15–1.58)
K_a (h^{-1})	0.23 (0.19–0.28)	0.52 (0.44–0.59)
$t_{1/2}\beta$ (h)	10.35 (9.39–11.32)	18.17 (14.10–22.23)
β (h^{-1})	0.068 (0.061–0.075)	0.039 (0.032–0.047)
$AUC^{0-\infty}$ ((ng h)/ml)	175.25 (145.74–204.75)	481.19 (252.87–709.51)
Cl_T/F (ml/(min kg))	2.61 (2.34–2.88)	–
Vd/F (l)	178.78 (146.46–211.10)	–

–, Not determined.

Table 3
Urinary excretion of lorazepam and its metabolite glucuronide in parturients treated with a single oral dose of 2 mg rac-lorazepam; mean (CI 95%)

	Lorazepam isomeric mixture	Lorazepam-glucuronide isomeric mixture
A_e total (μg)	8.18 (2.67–13.70)	899.77 (534.58–1265.0)
Fel (%)	0.29 (0.12–0.45)	44.97 (26.65–63.29)
Cl_R (ml/(min kg))	0.0099 (0.0049–0.015)	1.12 (0.69–1.55)
$t_{1/2}$ (h)	12.75 (10.71–14.79)	11.5 (6.14–16.86)
Kel (h^{-1})	0.057 (0.048–0.065)	0.066 (0.040–0.093)

Table 4
Transplacental distribution of lorazepam as an enantiomeric mixture at delivery ($n = 8$)

Parturient	Cord blood (ng/ml)	Maternal blood (ng/ml)	Collection time[a] (min)	Cord blood/maternal blood
1	5.77	14.74	135	0.392
2	6.82	7.95	426	0.858
3	4.38	10.48	153	0.418
4	8.42	9.60	300	0.878
5	5.87	5.33	390	1.100
6	5.78	9.87	120	0.586
7	7.75	10.94	552	0.708
8	9.45	10.35	207	0.913
Mean CI 95%	6.78 (5.39–8.17)	9.91 (7.68–12.14)	293.4 (163.2–423)	0.73 (0.52–0.94)

Parturients were treated with a single oral dose of 2 mg rac-lorazepam; mean (CI 95%).
[a] Time between drug intake and blood collection from the umbilical cord and maternal vein.

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Table 3

Pharmacokinetic parameters of lorazepam (LZP) following administration of a single dose (0.1 mg kg^{-1}) either intravenously (i.v.) or intramuscularly (i.m.) in children with severe malaria and convulsions

Parameter	*n*	I.v. LZP	*n*	I.m. LZP	95% CI for the difference between the means or medians
C_{max} (ng ml^{-1})	11	65.1 (47.5, 86)	10	45.3 (29.6, 66.3)	–43.5, 5.0
t_{max} (h)*	11	0.5 (0.167–0.67)	10	0.42 (0.167–1.0)	–0.33, 0.17
$t_{1/2}$ (elimination), h	9	23.7 (9.8, 37.6)	5	36.9 (–1.5, 75.5)	–41.3, 14.9
$AUC_{0-\infty}$ (ng ml^{-1} h^{-1})	9	2062.5 (600.6, 3771.4)	5	1843.6 (296.7, 3390.5)	–1267.8, 1883.0
k_a (h^{-1})*		–	6	9.8 (0.033, 22.8)	–
$t_{1/2}$ (absorption), h*		–	6	0.035 (0.01, 0.071)	–
CL (l h^{-1})	9	0.64 (0.36, 0.92)		–	–
V_C (l kg^{-1})	9	1.67 (1.25, 2.10)		–	–
V_{ss} (l kg^{-1})	9	2.59 (1.56, 3.62)		–	–
Bioavailability (*F*)	9	Assume 100%	6	89.4%	–

Values are presented as mean (95% CI) or median (range)*.

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TableII. NC pharmacokinetic parameters from elective cohort patients

	C_{max} (ng/mL)	$AUC_{0-\infty}$	CL (mL/min/kg)	CL (mL/min/m^2)	Vdz (L/kg)	$T_{1/2}$ (hours)
n	15	15	15	15	15	15
Range	29.3-209.6	253.3-3202.5	3.33-131.50	5.5-67.5	0.33-4.05	9.5-47.0
Mean ± SD	56.1 ± 44.9	822.5 ± 706.1	49.33 ± 30.83	31.95 ± 13.99	1.92 ± 0.84	20.5 ± 10.2
Median	42.2	601.5	41.50	32.34	1.94	18.1

C_{max}, maximum concentration; *$AUC_{0-\infty}$*, area-under-the-curve to infinity; *Vdz*, apparent volume of distribution.

Table 3

Bayesian pharmacokinetics parameters (all subjects). CL is clearance. Vdss is volume of distribution at steady state. Beta is the terminal slope of the log concentration versus time profile. $T_{½}$ Beta is the elimination half-life.

	Free Fraction	CL (mL/min/kg)	CL mL/min/m^2)	Vdss (L/kg)	Beta (hr^{-1})	$T_{½}$ Beta (hr)
Overall						
N	61	63	63	63	63	63
Range	0.07–0.48	0.3–7.75	6.50–147.17	0.49–3.40	0.017–0.118	5.9–42.0
Mean ± s.d.	0.10 ± 0.05	1.2 ± 0.93	33.33 ± 19.33	1.48 ± 0.54	0.048 ± 0.020	16.8 ± 7.1
Median	0.09	1.08	29.00	1.37	0.046	15.1
3 Month to < 3 Years						
N	17	18	18	18	18	18
Range	0.07–0.48	0.63–7.75	12.83–147.17	0.67–3.40	0.024–0.118	5.9–28.4
Mean ± s.d.	0.11 ± 0.10	1.57 ± 1.62	32.83 ± 30.17	1.62 ± 0.59	0.053 ± 0.027	15.8 ± 6.5
3 to < 13 Years						
N	28	29	29	29	29	29
Range	0.07–0.17	0.30–1.82	6.50–69.17	0.49–3.00	0.017–0.092	7.5–40.6
Mean ± s.d.	0.10 ± 0.02	1.12 ± 0.40	31.83 ± 13.83	1.50 ± 0.61	0.048 ± 0.017	16.9 ± 7.4
13 to < 18 Years						
N	16	16	16	16	16	16
Range	0.07–0.15	0.43–1.58	16.33–60.00	1.00–1.54	0.017–0.084	8.2–42.0
Mean ± s.d.	0.09 ± 0.02	0.95 ± 0.32	36.67 ± 12.00	1.27 ± 0.17	0.044 ± 0.016	17.8 ± 7.7

TABLE 2 Fentanyl concentrations in umbilical vein and maternal serum. Data are presented as mean (SD) or median [interquartile range] as appropriate

Variable	Adrenaline group (n = 19)	Control group (n = 20)	Mean difference	*P*-value
Mean serum fentanyl concentration, umbilical vein (nmol/L)	0.162 (0.090) (n = 16)	0.151 (0.070) (n = 20)	0.012 [−0.042; 0.065]	.67
Median maternal serum fentanyl concentration at birth (nmol/L)	0.268 [0.193; 0.493][a] (n = 16)	0.291 [0.212; 0.502][a] (n = 19)	−0.061 [−0.205; 0.082]	.66[a]
Mean AUC 0-120 min for fentanyl in maternal serum (nmol h/L)	0.428 (0.162) (n = 18)	0.590 (0.197) (n = 15)[b]	−0.162 [−0.289; −0.034]	.015

AUC, Area under the curve. Student's *t* test was used to calculate *P*-values unless otherwise specified. Complete case analysis, numbers in some cells lower than the total numbers of patients included due to missing data (hemolysis of samples, technical laboratory difficulties).

[a]Mann–Whitney *U* test used. Data presented as median [25th; 75th percentile].

[b]Two cases with missing data due to birth prior to 120 min sample.

Table 3. Ketamine Estimated Pharmacokinetic Parameters in Children Population (Values are Mean ± SD)

Parameter	Unit	Value
Total area under curve	Mg/min/L	91 ± 30
Maximum concentration	mg/L	1.6 ± 0.68
Total body clearance	L/min	0.52 ± 0.26
Body weight normalized clearance	L/kg/min	0.025 ± 0.008
Mean residence time	hr	2.3 ± 0.64
Distribution volume at steady state	L	69 ± 39
Body weight normalized distribution volume	L/kg	3.3 ± 1.3
Elimination half-life	hr	2.6 ± 1

PK parameters	Dose range 1 (5–15 mg/kg/12 h)			Dose range 2 (15–25 mg/kg/12 h)			Dose range 3 (25–35 mg/kg/12 h)		
	Historical data[a]	Current data	p value[b,c]	Historical data[a]	Current data	p value[b,c]	Historical data[a]	Current data	p value[d]
C_{max} (μg/mL)	24.8 ± 8.3	19.19 ± 4.12	0.07	57.1 ± 14.9	35.12 ± 10.54	0.001	73.2 ± 19.2	36.11 (27.58–44.64)[e]	–
AUC_{0-12} (h*μg /mL)	145 ± 44	167.0 ± 45.6	0.26	322 ± 71	316.5 ± 108.4	0.88	433 ± 94	290.9 (176.14–405.59)[e]	–
C_{trough} (μg/mL)	8.4 ± 3.8	9.99 ± 3.86	0.34	15.6 ± 5.3	19.25 ± 8.48	0.22	20.6 ± 5.8	13.03 (2.98–23.07)[e]	–
T_{max} (h)	0.5 (0.25–3.0)[e]	1.5 (1.5–2.5)[e,f]	–	0.5 (0.5–3.0)[e]	2.5 (2.0–3.3)[e,f]	–	0.5 (0.5–3)[e]	1.5 (1.5)[e,f]	–

C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration; AUC_{0-12}, area under the curve from time 0 to 12 h; C_{trough}, trough plasma concentration.
[a]Compared with historical data by Fountain, *et al.* [18].
[b]Compared with historical data.
[c]*T*-test used to assess data.
[d]Too small sample to compare to historical data.
[e]Median (range); all other data expressed as mean (±standard deviation).
[f]Non-normally distributed data.

TABLE 3 ***Comparison of pharmacokinetic parameters between participants receiving levetiracetam via naso- or orogastric tube vs. participants receiving the drug orally***

Pharmacokinetic parameter	Naso- or orogastric tube administration, $n = 14/19$	Oral administration, $n = 5/19$	P value[a]
AUC_{0-12} (h*μg/mL)	220 (157.5–355.4)	213.8 (154.0–348.8)	0.90
C_{max} (μg/mL)	23.8 (18.8–41.3)	26.4 (19.3–34.2)	0.84
T_{max} (h)	1.5 (1.5–2.5)	2.5 (1.5–2.9)	0.46

All values expressed as medians and interquartile ranges. Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}) and area under the curve 0–12 h (AUC_{0-12}).
[a]The study was not powered to specifically compare naso- or orogastric administration vs. oral administration.

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Table 2.

Summary of pharmacokinetic (PK) parameters of isoniazid, rifampicin and pyrazinamide among Indonesian children treated for TBM

PK parameters	First PK assessment (n=20)	Second PK assessment (n=12)	P value*
Isoniazid			
AUC_{0-24} (h·mg/L)	18.5 (5.1–47.4)	14.5 (5.9–44.2)	0.888
C_{max} (mg/L)	4.6 (1.0–10.0)	4.7 (2.5–13.6)	0.366
C_{CSF0-2} (mg/L)†	1.4 (0.5–6.1)	1.6 (1.2–2.5)	n/a
C_{CSF3-5} (mg/L)†	1.6 (0.3–5.0)	1.7 (0.6–5.0)	n/a
C_{CSF6-8} (mg/L)†	1.3 (1.2–4.3)	2.3 (1.9–2.8)	n/a
Rifampicin			
AUC_{0-24} (h·mg/L)	66.9 (21.7–118.6)	71.8 (36.1–116.5)	0.442
C_{max} (mg/L)	9.4 (2.9–23.7)	10.4 (5.7–23.3)	0.499
C_{CSF0-2} (mg/L)†	0.2 (0.1–0.4)	0.1 (0.1–0.1)	n/a
C_{CSF3-5} (mg/L)†	0.3 (0.1–0.8)	0.1 (0.1–0.3)	n/a
C_{CSF6-8} (mg/L)†	0.4 (0.1–1.4)	0.2 (0.1–0.7)	n/a
Pyrazinamide			
AUC_{0-24} (h·mg/L)	315.5 (100.6–599.0)	328.4 (143.3–1477.7)	0.482
C_{max} (mg/L)	37.7 (15.9–61.7)	40.5 (22.7–88.4)	0.350
C_{CSF0-2} (mg/L)†	24.4 (11.1–54.9)	25.6 (21.3–37.1)	n/a
C_{CSF3-5} (mg/L)†	30.0 (19.2–43.3)	24.7 (15.9–38.1)	n/a
C_{CSF6-8} (mg/L)†	19.6 (7.2–37.7)	39.4 (23.1–70.8)	n/a

Data are presented as geometric mean (range). The first PK assessment was performed on day 2 of treatment and the second PK assessment was performed on day 10 of treatment.

*Paired-sample t-test on log-transformed data of 12 patients for whom PK data were available both at the first and second PK assessments.

†At the first PK assessment, 6, 7 and 7 CSF samples for each drug were available at 0–2 hours, 3–5 hours and 6–8 hours, respectively; and at the second PK assessment, 4, 4 and 3 CSF samples for each drug were available at 0–2 hours, 3–5 hours and 6–8 hours, respectively.

AUC_{0-24}, area under the plasma concentration–time curve from 0 to 24 hours postdose; C_{CSF0-8}, drug concentration in cerebrospinal fluid during 0–8 hours postdose; C_{max}, peak plasma concentration; n/a, non-applicable; TBM, tuberculous meningitis.

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TABLE 2.

Vancomycin exposure before and after implementation of the vancomycin dose-optimization protocol

Factor	Data for:[a]		*P* value
	Before group	After group	
Initial Cavg	*n* = 60	*n* = 59	
Repartition[b]			
Subtherapeutic	41 (68.3)	6 (10.2)	<0.001
Therapeutic	17 (28.3)	44 (74.6)	<0.001
Supra-therapeutic	2 (3.3)	9 (15.3)	0.001
Concentration (mg/L)	12.9 [11.3–17.0]	20.3 [17.0–22.2]	<0.001
All Cavg	*n* = 116	*n* = 103	
Repartition[b]			
Subtherapeutic	78 (67.2)	13 (12.6)	<0.001
Therapeutic	36 (31.0)	77 (74.8)	<0.001
Supra-therapeutic	2 (1.7)	13 (12.6)	0.025
Concentration (mg/L)	13.1 [11.3–16.2]	19.8 [16.8–22.1]	< 0.001
Initial Cavg/MIC ratio	*n* = 22	*n* = 17	
Repartition			
<8	10 (45.5)	2 (11.8)	0.02
≥8	12 (54.5)	15 (88.2)	
Cavg/MIC ratio	8.8 [6.2–11.5]	12.8 [10.9–20.9]	0.004
Initial AUC/MIC ratio	*n* = 22	*n* = 17	
Repartition			
<400	20/22 (90.9)	10/17 (58.8)	0.02
≥400	2/22 (9.1)	7/17 (41.2)	
AUC/MIC ratio	211 [149–275]	307 [262–502]	0.006

[a]Data are reported as *n* (%) or medians [25th to 75th percentiles].

[b]Therapeutic range, Cavg between 15 and 25 mg/L; subtherapeutic, Cavg < 15 mg/L; supra-therapeutic, Cavg > 25mg/L. Cavg, average concentration; AUC, area under the curve.

Table 2
Comparisons of unbound plasma meropenem concentrations classified by patients without and with augmented renal clearance.

	Patients without ARC GM (95% CI)	Patients with ARC GM (95% CI)	*P*-value[a]
EI	$N = 28$	$N = 26$	
C_{mid} (mg/L)	19.9 (13.5–29.5)	14.8 (11.4–19.1)	0.20
C_{trough} (mg/L)	3.5 (2.0–6.1)	1.6 (1.0–2.6)	0.04
IB	$N = 11$	$N = 7$	
C_{mid} (mg/L)	4.9 (2.6–9.2)	1.9 (0.4–9.6)	0.14
C_{trough} (mg/L)	0.8 (0.4–1.6)	0.9 (0.2–4.2)	0.85

Data are shown as geometric mean (95% CI).

[a] *P*-value of two-sample independent t-test.ARC = augmented renal clearance (eGFR $\geq$ 130 mL/min/1.73 m^2); CI = confidence interval; C_{mid} = unbound plasma meropenem concentrations at mid-dosing intervals; C_{trough} = unbound plasma meropenem concentrations at end-dosing intervals; EI = extended infusion; GM = geometric mean; IB = intermittent bolus.