

Supplementary Table S1. Parameter estimates and characteristics of studies from adults and children given diamorphine

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	T _{max} (min)
Bourquin 1999	Noncompartmental analysis	5	1	/	/	IV bolus	200	DAM	/	/	2.3 ±0.4	3380 ±2737	2.5 ±1.5
								6-AM	/	/	23.4 ±13.4	2670 ±1309	2.5 ±1.6
								MOR	/	/	/	447 ±79.5	7 ±7.6
								M6G	/	/	/	751 ±168	64.5 ±31
Cone 1993	PKCALC ⁱ	6	1	27.8 ±3.3	74.5 ±6.1	IM	6	DAM	/	/	7.8 ±4.2	/	<5
								6-AM	/	/	11.4 ±5.4	/	5-10
								MOR	/	/	66 ±72	/	<60
								Intranasal	6	DAM	/	/	5.4 ±3
						6-AM	/	/		10.8 ±8.4	/	5-10	
						MOR	/	/		90 ±96	/	<60	
						12	DAM	/		/	4.2 ±1.2	/	<5
							6-AM	/	/	13.2 ±8.4	/	5-10	

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
								MOR	/	/	168 ±216	/	<90
Girardin 2003	(S)-Plus program	8	1	32 (range: 24-39)	64 (range: 43-85)	IM	77 ±17	DAM	/	/	/	1329.9 ±701.9	6 ±2
								6-AM	/	/	/	425.6 ±229.2	6 ±2
								MOR	/	/	/	313.9 ±313.9	23 ±17
								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
							155 ±35	DAM	/	/	/	2807.5 ±1182.1	5 ±2
								6-AM	/	/	/	785.7 ±523.8	7 ±1
								MOR	/	/	/	485.1 ±456.5	17 ±11
								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
							233 ±35	DAM	/	/	/	3287.8 ±886.6	4 ±2
								6-AM	/	/	/	1113.1 ±425.6	6 ±2

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
								MOR	/	/	/	485.1 ±228.3	17 ±6
								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
						IV	146 ±48	DAM	37 ±16	11.6 ±2.8	3 ±1	3952.7 ±1366.8	0.3 ±0.2
								6-AM	/	/	3 ±1	5729.0 ±1833.3	0.3 ±0.1
						Oral	206 ±50	DAM	/	/	/	/	/
								6-AM	/	/	/	/	/
								MOR	/	/	/	370.9 ±199.7	37 ±27
								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
							413 ±99	DAM	/	/	/	/	/
								6-AM	/	/	/	/	/
								MOR	/	/	/	798.9 ±428.0	53 ±25

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								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
							619 ±149	DAM	/	/	/	/	/
								6-AM	/	/	/	/	/
								MOR	/	/	/	1084.3 ±656.3	63 ±53
								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
Gyr 2000	Topfit 2.0, noncomparmental model, AUC calculated by linear	V 2	1	28 ±4.2	56 ±2.8	IV bolus	200	DAM	61.1 ±2.5	25.95 ±8.6	1.75 ±0.6	1900 ±523.3	1.3 ±0.3
								6-AM	/	/	48.95 ±4.13	4010 ±862.7	1.1 ±0.6
								MOR	/	/	234.5 ±74.2	575 ±332.3	3.75 ±0.2
								M3G	/	/	362.5 ±27.6	3305 ±318.2	90.65 ±40.1

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
	trapezoidal rule							M6G	/	/	672.5 ±12.0	985 ±403.1	80.8 ±54.0
						Oral	400 (1 st dose)	MOR	/	/	274 ±5.7	1035 ±431.3	90.55 ±43.1
								M3G	/	/	194 ±28.3	7185 ±360.6	179.5 ±84.1
								M6G	/	/	157.5 ±40.3	1705 ±332.3	179.5 ±84.1
							400 (2 nd dose)	MOR	/	/	376 ±17.0	910 ±254.6	76.6 ±64.2
								M3G	/	/	1079 ±1118.6	6850 ±1244.5	121.5 ±0.7
								M6G	/	/	1486.5 ±1786.9	1560 ±42.4	121.5 ±0.7

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	T _{max} (min)
							460 (1 st dose, CR)	MOR	/	/	/	520 ±127.3	104.2 ±104.4
								M3G	/	/	/	4775 ±643.5	148.5 ±41.7
								M6G	/	/	/	1185 ±134.4	179 ±84.9
							690 (2 nd dose, CR)	MOR	/	/	/	1420 ±353.6	61.6 ±3.1
								M3G	/	/	/	575 ±49.5	119 ±0
								M6G	/	/	/	6355 ±700.0	420 ±425.7
						Rectal	400 (1 st dose)	MOR	/	/	379 ±323.9	540 ±84.9	36.3 ±5.2
								M3G	/	/	232 ±0	8055 ±5013.4	49.35 ±23.7
								M6G	/	/	171.5 ±50.2	2535 ±445.5	93.2 ±43.6
							400 (2 nd dose)	MOR	/	/	20.15 ±0.2	600 ±70.7	20.15 ±0.2

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
								M3G	/	/	270.5 ±14.8	7790 ±2135.5	45.1 ±20.8
								M6G	/	/	241.5 ±20.5	1940 ±70.7	59.85 ±0.1
Halbsguth 2008	(S)-Plus program	8	2	35 (range: 26-46)	73 (range: 60-88)	Oral	18.1	MOR	/	/	/	74.9736 ±17.3016	9 ±2
		8	3	30 (range: 21-42)	76 (range: 54-106)			M3G	/	/	/	/	/
								M6G	/	/	/	/	/
								MOR	/	/	/	28.836 ±23.0688	20 ±14
								M3G	/	/	/	/	/
								M6G	/	/	/	/	/
Inturrisi 1984	Noncompartmental	11	4	49.7 (range:)	/	IV bolus	4-16	DAM	/	/	3.0 ±1.3	/	/
						IM	4	DAM	/	/	/	/	10

Study	PK calculation analysis	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
				30-65)				6-AM	/	/	/	/	10
								MOR	/	/	/	/	15
						IV infusion ⁱⁱ	20-60	DAM	20.16	2.2 ±0.1		91.4 ±42.6	/
								6-AM	/	/	/	15	/
								MOR	/	/	/	30	/
Jenkins 1994	Noncompartmental analysis	2	5	35 (range: 32-38)	/	Inhalation	2.6-10.5	DAM	100.2 ±93.5	20.9 ±19.7	3.3 ±1.8	126.2 ±98.7	2.3 ±1.4
								6-AM	/	/	5.4 ±1.7	54.8 ±46.9	1.8 ±0.4
								MOR	/	/	18.8 ±14.3	19.12 ±20.4	3.23 ±2.5
						IV	3-20	DAM	66.1 ±31.6	11.4 ±4.8	3.6 ±1.4	198.7 ±151.5	2 ±0
								6-AM	/	/	9.3 ±8.9	131.5 ±114.0	2.6 ±1.3
								MOR	/	/	108.7 ±107.5	46.1 ±38.5	3.8 ±1.6

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
						SC	5	DAM	46.2	7	4.6	42	10
								6-AM	/	/	12	32.9	10
								MOR	/	/	39.6	12.7	10
Klous 2005	WinNonlin, noncomparmental analysis, AUC by log-linear interpolate trapezoid rule	5	1	36.2 (range: 30-48)	65 (range: 51-89)	Inhalation (by Chasing the dragon)	50	DAM	/	/	/	225.34071 ±132.98796	1
								6-AM	/	/	/	173.50822 ±91.66472	1
								MOR	/	/	143 ±67.9	±34.24056	120
								M3G	/	/	280.1 ±81.7	±166.12632	2
								M6G	/	/	269.9 ±123.4	±24.8746	2
						Inhalation	50	DAM	/	/	/	44.32932	1

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
						(by heating device)						±22.16466	
												52.37984	
								6-AM	/	/	/	±26.18992	1
												37.09394	
								MOR	/	/	127 ±36.7	±25.68042	120
												230.731	
								M3G	/	/	252 ±47.6	±92.2924	2
												39.79936	
								M6G	/	/	216.2 ±35	±18.45848	2
Kotob 1986	AUC: trapezoidal, t _{1/2} : linear regression	10	6	67 ±3.7	62 ±2.9	Intrathecal	1			0.00063		54878.0	
								DAM	/		43 ±13.2	±20960.2	5
								MOR	/	/	/	13.6 ±8.1	10 ±7.6
Mitchell 2006	Noncompartmental	4	2	/	/	Intranasal		6-AM	/	/	/	525 ±654	13 ±3
							40	MOR	/	/	/	225 ±128	15 ±4.1

Study	PK calculation analysis	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
						IV		6-AM	/	/	/	1860 ±1372	2 ±0
							40	MOR	/	/		335 ±158	2 ±0
Moore 1984	NONLIN	3	6	/	/	Intrathecal	2		0.003	0.0014		545496.9	
								DAM	±0.001	±0.0004	7.43 ±0.99	±160782.2	/
Moreno-Vicente 2015	Noncompartmental analysis by Phoenix WinNonlin 6.3	12	7	/	/	Oral	50		637.3				
								MOR	±103.1	10.7 ±2.8	42 ±12	85.1 ±23.7	24 ±12
									159.4				
								M3G	±37.9	0.2 ±0	732 ±162	1165 ±227	42 ±18
									352.2				
								M6G	±169.3	1 ±0.1	252 ±144	251 ±38.2	54 ±12
Perger 2009	Noncompartmental, deconvolut	8	1	37 (range: 28-50)	62.3 (range: 59-	Oral (IR)	719					1141.352	
								MOR	/	/	/	±362.37926	76 ±52
								M3G	/	/	/	/	/

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)	
	ion analysis				84.5)	Oral (ER, fasted state)	356	M6G	/	/	/	/	/	/
								MOR	/	/	/	±490.78136	157 ±71	
								M3G	/	/	/	/	/	
								M6G	/	/	/	/	/	
						Oral (ER, fed state)	356	MOR	/	/	/	±302.45828	263 ±33	
								M3G	/	/	/	/	/	
								M6G	/	/	/	/	/	
Rentsch 2001	Nonparametric deconvolution analysis	8	1	35 (range: 31-40)	69 (range: 56-85)	IV bolus	57-171		20 ±14 ^a	8.7 ±2.6 ^a	2.4 ±0.8 ^a	/	0.4 ±0.2 ^a	
								DAM	70 ±29 ^b	13.7 ±4.2 ^b	3.3 ±1.2 ^b	/	2.8 ±1.4 ^b	
									/	6.7 ±1.6 ^a	/	/	0.4 ±0.2 ^a	
								6-AM	/	9.4 ±3.5 ^b	/	/	2.7 ±1.4 ^b	

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	T _{max} (min)
							57	DAM	/	/	/	/	/
								6-AM	/	/	/	/	/
							144	DAM	/	/	/	/	/
								6-AM	/	/	/	/	/
							171	DAM	/	/	/	/	/
								6-AM	/	/	/	/	/
Rook 2006	Noncompartmental analysis by WinNonlin 3.0	9	1	45 (range: 34-48)	73 (range: 62-132)	Inhalation	167.5-375		76.9				
								DAM	±21.6	16.9 ±3.7	3.24 ±0.78	/	/
									567.5				
								6-AM	±100.0	15.9 ±3.0	25.59 ±2.55	/	/
								MOR	/	/	184.3 ±21.5	/	/
								M3G	/	/	282.8 ±30.2	/	/
								M6G	/	/	240.3 ±25.1	/	/

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	T _{max} (min)
							167.5	DAM	/	/	/	628.0 ±254.9	/
								6-AM	/	/	/	196.4 ±68.7	/
								MOR	/	/	/	191.2 ±599.2	/
								M3G	/	/	/	1684.3 ±623.0	/
								M6G	/	/	/	304.6 ±83.1	/
							250	DAM	/	/	/	683.4 ±254.9	/
								6-AM	/	/	/	288.1 ±58.9	/
								MOR	/	/	/	271.1 ±59.9	/
								M3G	/	/	/	2284.2 ±498.4	/
								M6G	/	/	/	461.4 ±96.9	/
							375	DAM	/	/	/	1045.4 ±1063.9	/
								6-AM	/	/	/	389.6 ±157.1	/

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	Tmax (min)
								MOR	/	/	/	376.6 ±128.4	/
								M3G	/	/	/	3151.8 ±1218.3	/
								M6G	/	/	/	669.2 ±249.2	/
				40 (range: 32-54)	73 (range: 57-101)	IV	175-394		96				
								DAM	±76.1	15.5 ±3.7	3.8 ±1.3	/	7.8 ±21.5
									325				
								6-AM	±70.2	10.1 ±1.2	22.0 ±2.8	/	2
								MOR	/	/	176.8 ±18.8	/	/
								M3G	/	/	275.9 ±20.5	/	60
								M6G	/	/	267.6 ±30.0	/	60
								DAM	/	/	/	2785.4 ±1188.4	/
								6-AM	/	/	/	1247.3 ±488.6	/
							175.875	MOR	/	/	/	545.0 ±132.5	/

Study	PK calculation	Participants (n)	Clinical category	Age (year)	Weight (kg)	Route	DAM dose (mg)	Chemical	Vd (L)	CL (L/min)	t _{1/2} (min)	C _{max} (ng/ml)	T _{max} (min)
								M3G	/	/	/	3193.3 ±551.0	/
								M6G	/	/	/	456.8 ±244.9	/
								DAM	/	/	/	3114.1 ±735.1	/
								6-AM	/	/	/	1728.5 ±423.5	/
								MOR	/	/	/	827.5 ±123.0	/
								M3G	/	/	/	4287.0 ±719.3	/
							262.5	M6G	/	/	/	678.3 ±199.0	/
								DAM	/	/	/	3502.0 ±1286.5	/
								6-AM	/	/	/	2625.5 ±1172.6	/
								MOR	/	/	/	1349.6 ±397.5	/
							393.75	M3G	/	/	/	6788.1 ±1867.2	/

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Skopp 1997	AUC: trapezoidal, t _{1/2} : linear regression	4	5	34.8 ±6.1	69.8 ±8.1	IM	6	M6G	/	/	/	1001.4 ±459.1	/
								DAM	/	/	5.4	/	/
								6-AM	/	/	19.2	/	/
								MOR	/	/	102 ±17	7.9	10.2
								M3G	/	/	141 ±55	92.6 ±0.6	20.1 ±14.0
								M6G	/	/	/	/	/
								DAM	/	/	5.1 ±1.1	25.75 ±13.7	6.5 ±4.2
								6-AM	/	/	23.7 ±5.0	8.3375 ±5.1	7.8 ±2.7
								MOR	/	/	133.5 ±36.1	8.6 ±3.7	43.7 ±33.4
M3G	/	/	188 ±65.4	80.9 ±40.3	95.6 ±63.1								
M6G	/	/	/	22.9 ±1.4	105 ±21.2								

Abbreviations:

AUC: area under the curve, CL: clearance, C_{max}: maximal concentration, t_{1/2}: half-life, Tmax: time-point Cmax, Vd: distribution volume, IV: intravenous

Route:

IV: intravenous, IM: intramuscular

Subject category:

1: Heroin-addicted patients, 2: opioid-dependent patients, 3: opioid-naïve patients, 4: patients with chronic pain, 5: healthy volunteers with history of heroin use, 6: post-operative patients, 7: healthy volunteers in clinical trials, 8: children presented to A&E with deformed fractured long bone, 9: premature neonates

Dose:

CR: controlled-release, IR: immediate-release, ER: extended-release

Chemical:

DAM: heroin, 6-AM: 6-monoacetylmorphine, MOR: morphine, M3G: morphine-3-glucuronide, M6G: morphine-6-glucuronide

Vd: a: arterial, b: venous

CL: a: arterial, b: venous

t_{1/2}: a: arterial, b: venous

AUC:

a: 0-300 minutes, b: 0-∞, c: 0-720 minutes, d: 0-1440 minutes, e: 0-360 minutes, f: 0-60
