13

Animal Physiology

A thorough understanding of animal physiology is a prerequisite for conducting pharmacokinetic studies and interpreting data in an appropriate way. This chapter presents data relating to animal physiology and recommendations for dosing in common laboratory animals. Table 13.1 summarizes physiological and biochemical parameters in animals, which can be used when designing studies in pharmacokinetics and metabolism with various laboratory animals and humans, and interpreting the results. Tables 13.2 and 13.3 summarize the information on drug administration in laboratory animals in terms of needle size and maximum dosing volume depending on the route of administration. Table 13.4 details the physiology of the rat, which is the most commonly used species in pharmacokinetic studies, and Table 13.5 can be used as a guideline for anesthesia in rats. Figure 13.1 illustrates the chemical composition of extracellular and intracellular fluids and the physiological differences between them, which can be of help in understanding the pharmacokinetic behavior of endogenous and exogenous substances at the cellular level.

Table 13.1. Important Physiological and Biochemical Parameters in Laboratory Animals and Humans

Species	Mouse	Hamster	Rat	Guinea pig	Rabbit	Cat	Monkey	Dog	Man	Note[a]
Body weight (kg, male)	0.02–0.06	0.11–0.14	0.25–0.4	0.6–1	2.5–6	2–4	5	10	70	1
Body surface area (m^2)	0.008	—	0.023	—	0.17	—	0.32	0.51	1.85	2
	0.004	0.026	0.033	0.06–0.07	0.13–0.30	—	—	—	—	3
Body temperature (°C)	36.5–38.0	37–38	37.5–38.5	38–40	38.5–39.5	38–39.5	36–40	38–39	37.0	3
Daily consumption										
Food (g/kg)	100–200	100	100	30–50	25–50	40–80	50–60	25	—	3
Water (ml/kg)	150	80–100	100–120	100	60	50	—	25–40	—	
Gestation (days)	17–21	15–16	20–23	58–75	30–35	58–71	150–183	53–71	—	
	avg. 19	avg. 15.5	avg. 21	avg. 68	avg. 31	avg. 65	avg. 165	avg. 63	—	
Birth weight (g)	0.5–1.5	2–3	5	70–100	30–100	90–130	450–500	200–500	—	3
Life span (yr)	1–2	2–3	2–3	5–6	5–6	10–17	20–30	10–15	—	3
Organ weight (g)										
Adrenals	0.004	0.027	0.05	—	0.5	—	1.2	1	14	2, 4, 5
Brain	0.36	—	1.8	—	14	—	90	80	1400	italic for
Fat	—	—	—	—	—	—	—	—	10,000	organ
Heart	0.08	0.46	1.0	—	5	—	18.5	80	330	volume
Intestine	*1.5*	*12.23*	*11.25*	—	*120*	—	*230*	*480*	2100	(ml)
Kidneys	0.32	0.96	2.0	—	13	—	25	50	310	
Liver	1.75	6.05	10.0	—	77	—	150	320	1800	
Lung	0.12	0.74	1.5	—	18	—	33	100	1000	
Marrow	*0.6*	—	—	—	*47*	—	*135*	*120*	*1400*	
Spleen	0.1	*0.54*	0.75	—	1	—	8	25	180	
Body Fluids										
Blood (ml/kg)	74.5	72.0	58.0	74.0	69.4	84.6	75.0	92.6	77.8	2
Hematocrit (%)	45	37	46	48	36	44	41	42	44	
Blood pH	—	7.39	7.38	7.35	7.35	7.35	—	7.36	7.39	6
Plasma (ml/kg)	48.8	45.5	31.3	38.8	43.5	47.7	44.7	53.8	47.9	2

Plasma protein (mg/ml plasma)										
Plasma albumin	32.7	—	31.6	—	38.7	—	49.3	26.3	41.8	2, 6
Plasma α-1-ACG	12.5	—	18.1	—	1.3	—	2.4	3.7	1.8	
Total	62	—	67	47	57	—	88	90	74	
Cerebrospinal fluid										
Volume (μl/g tissue)	—	—	—	—	—	—	—	4.9	22.4	7
Flow (μl/min)	—	—	2.2	—	10.1	22	—	47	429	
Interstitial fluid (ml/kg)	—	—	—	—	—	—	—	—	157.1	8
Intracellular fluid (ml/kg)	—	—	—	—	—	—	—	—	400.0	
Total body water (ml/kg)	—	—	—	—	—	—	—	—	600.0	
Blood flow (ml/min)										
Adrenal	—	—	—	—	—	—	—	—	100	
Adipose	—	—	0.4	—	32	—	20	35	260	2, 5
Brain	—	—	1.3	—	—	—	72	45	700	italics for
Heart	0.28	*0.14*	3.9	—	16	—	60	54	240	plasma
Hepatic artery	0.35	—	2.0	—	37	—	51	79	300	flow rate
Intestine	1.5	*5.3*	7.5	—	111	—	125	216	1100	
Kidneys	1.3	*5.27*	9.2	—	80	—	138	216	1240	
Liver	1.8	*6.5*	13.8	62	177	—	218	309	1450	
Lung	—	*28.4*	—	—	—	—	—	—	1400	
Marrow	*0.17*	—	—	—	*11*	—	*23*	*20*	*120*	
Muscle	0.91	—	7.5	—	155	—	90	250	750	
Portal vein	1.45	—	9.8	—	140	—	167	230	1150	
Skin	0.41	—	5.8	—	—	—	54	100	300	
Spleen	0.09	*0.25*	0.63	—	9	—	21	25	77	
Cardiac output	8.0	—	74.0	—	530	—	1086	1200	5600	
Blood in tissue (μl/g tissue)										
Adrenal gland	30	—	—	—	—	—	—	—	—	9
Bone	110	—	45	—	—	—	—	—	—	

Table 13.1 (Cont')

Table 13.1. Continued

Species	Mouse	Hamster	Rat	Guinea pig	Rabbit	Cat	Monkey	Dog	Man	Note[a]
Blood in tissue										
Bone marrow	—	—	—	55	—	—	—	—	—	
Brain	30	—	11	—	—	30	—	11	—	
Heart	—	—	60	—	—	84	—	66	—	
Intestine	90	—	28	—	—	—	—	41	—	
Kidney	340	—	92	—	—	93	—	81	—	
Liver	360	—	99	—	—	52	—	147	—	
Lung	490	—	111	—	—	147	—	301	—	
Skeletal muscle	30	—	4	—	—	27	—	11	—	
Skin	30	—	20	—	70	—	—	—	—	
Spleen	170	—	86	133	—	195	—	510	—	
Testis	60	—	6	—	—	—	—	—	—	
Heart rate (beats/min)	300–800	250–500	300–500	230–380	130–325	100–120	100–150	80–150	—	3
Bile flow	100	90	90	230	120	—	25	12	5	10
(ml/kg/day)	—	—	48–92	—	130	—	19–32	19–36	2.2–22.2	11
Bile pH	—	—	—	—	—	—	—	—	7.4–8.5	(hepatic duct bile)
									5.4–6.9	(gall bladder bile)
Bile concentration (relative to human)	0.05	0.06	0.6	0.02	0.04	—	0.2	0.23	1	10
Urine flow (ml/kg/day)	50	—	200	—	60	—	75	30	20	10
Urine concentration (relative to human)	0.4	—	0.1	—	0.34	—	0.26	0.66	1	10
Urine pH	—	—	—	—	—	—	—	—	6.3, 4.5–8.0	12
GFR (ml/min)	0.28	—	1.31	—	7.8	—	10.4	61.3	125	
	0.2	—	2.3	—	12	—	10.0	40	126	13
Number of glomeruli ($\times 10^5$/kg)	5.9	—	2.9	—	1.6	—	—	0.9	0.29	13

Lymph flow										
(ml/kg/day)										
Cervical duct	—	—	—	1.8	—	—	—	2.6	—	14
Heart	—	—	—	—	—	—	—	7.7	—	
Intestine	—	—	96	—	—	37	—	29	—	
Kidney	—	—	—	—	—	—	—	0.2, 2	—	
Leg	—	—	—	—	—	—	—	2.6	—	
Liver	—	—	7.7	—	—	18, 14	—	26, 36	—	
Lung	—	—	—	—	—	—	—	7, 10	—	
Right lymph duct	—	—	—	—	—	—	—	15, 21	—	
Thoracic duct	960	—	40, 96	39	30, 88	8, 40	—	55, 132	17, 144	
Thyroid gland	—	—	—	—	—	—	—	1.8	—	
Gastrointestinal (GI) tract										
Half gastric emptying	—	—	—	—	—	—	—	4–5	8–15	11, 15, 16
time (min)			(< 15)					(180)	(77–130)	
Intestinal transit										
time (min)										
Small intestine	—	—	88	—	—	—	—	111	238	2, 15, 17
									(275, > 600)	
Whole intestine	—	—	—	—	—	—	—	770	2350	2
								360–480	1200–1800	11
Intestine length (m)										
Small intestine	0.04	—	0.1–0.15	—	3.56	—	—	4.14	7	11, 18
Large intestine	—	—	0.02–0.03	—	2.26	—	—	0.74	—	
Intestine volume (ml)										
Whole intestine	1.5	12.23	11.25	—	120	—	230	480	2100	5
Gut lumen	1.5	—	8.8	—	—	—	230	—	2100	
Capacity (liters)										
Stomach volume	—	—	—	—	—	0.34	0.1	1	1–1.6	11
							(0.008)		(0.024)	basal
Small intestine	—	—	—	—	—	0.11	—	—	—	
Large intestine	—	—	—	—	—	0.12	—	—	—	
GI pH										
Saliva	—	—	—	—	—	—	—	—	6.0–7.0	19
Gastric juice	—	—	—	—	—	—	—	—	1.0–3.5	

Table 13.1 (Cont')

Table 13.1. Continued

Species	Mouse	Hamster	Rat	Guinea pig	Rabbit	Cat	Monkey	Dog	Man	Note[a]
GI pH										
Stomach	3.1–4.5	2.9–6.9	3.0–3.8	—	—	—	—	0.9–2.5	1.3–2.1	15, 20, 21
(fasted)	—	—	—	—	—	—	—	—	1.5–3.5	
(postprandial)	—	—	2.3–4.5	—	—	—	—	0.5–5.0	2.5–7.5	11, 22
Intestine	—	6.1–7.1	—	—	6.0–8.0	—	—	6.5–7.5	5.5–6.5	15, 20, 23
(fasted)	—	—	6.9–7.8	—	—	—	—	—	5–7	11, 22
(postprandial)	—	—	—	—	—	—	—	2–7	5–6	15
Pancreatic juice	—	—	—	—	—	—	—	—	8.0–8.3	19
Small intestinal secretion	—	—	—	—	—	—	—	—	7.5–8.0	
Large intestinal secretion	—	—	—	—	—	—	—	—	7.5–8.0	
Bile	—	—	—	—	—	—	—	—	7.8	
Feces	—	—	6.9	—	7.2	—	—	—	7.0–7.5	20, 24
Daily secretion (ml/kg/day)										
Saliva	—	—	—	—	—	—	—	—	14	19
Gastric juice	—	—	—	—	—	—	—	—	21	
Pancreatic juice	—	—	—	—	—	—	—	—	14	
Bile	—	—	—	—	—	—	—	—	14	
Small intestinal secretion	—	—	—	—	—	—	—	—	26	
Large intestinal secretion	—	—	—	—	—	—	—	—	2.9	
Metabolic Activities										
β-glucuronidase activity (nmol/hr/g content)										
Liver	2000–4000	2200	15,000–30,000	4500	5000	—	—	—	3000	25

Kidney	1000–4500	1100	4000–6000	600–1700	300	—	—	—	2000	
Lung	—	—	5000	—	—	—	—	—	500	
Spleen	4000–11000	—	15,000–30,000	5500	—	—	—	—	6500	
Brain	100	—	150	300	150	—	—	—	Trace	
Stomach	—	—	—	—	40	—	—	—	200–1000	
Small intestine	—	—	3000–5000	—	800	—	—	—	—	
Small intentinal content	1200	—	304	2.7	2.4	—	—	—	0.02	11, 26
	(5015)	—	(1341)	(139)	(45.4)	—	—	—	(0.9)	
Large intestine	—	—	3500	—	300	—	—	—	—	25
Large intestinal content	—	—	3000	—	2000	—	—	—	—	
Cytochrome P450	—	—	0.98	—	—	—	—	0.474	0.296	27
(nmol/mg protein)	—	—	(54)	—	—	—	—	(43)	(77)	

[a]Notes: (1) Average body weight for adult male animals. (2) Davies B. and Morris T., 1993. (3) Havenaar R. *et al.*, 1993. (4) Frank D. W., 1944. (5) Gerlowke L. E. and Jain R. K., 1983. (6) Altman P. L. and Dittmer D. S., 1971*a*. (7) Altman P. L. and Dittmer D. S., 1971*b*. (8) For an average man with 70 kg body weight, the plasma volume is 3 liters, the blood volume is 5.5 liters, the extracellular fluid outside the plasma (interstitial fluid) is 11 liters, the intracellular fluid is about 28 liters, and the total body water is approximately 42 liters (Benet L. Z. and Zia-Amirhosseini P., 1995). (9) Altman P. L. and Dittmer D. S., 1971*c*. (10) Clark B. and Smith D. A., 1982. (11) Kararli T. T., 1995. (12) Guyton A. C. and Hall J. E., 1996*a*. (13) Lin J. H., 1995. (14) Altman P. L. and Dittmer D. S., 1971*d*. (15) Dressman J. B., 1986. (16) Gastric half-emptying time after ingestion of water or normal saline (solid meal). In some studies in human, half-emptying time of the order of 30 min after a small meal has been reported, whereas after a large meal, it lasted up to 180 min. (17) Mean intestinal transit time of a Heidelberg capsule under fasting condition (tablet with heavy meal). There is more interindividual variation in transit time in dogs (15 to 206 min) than in humans (180 to 300 min), suggesting that drug absorption may be more variable and incomplete in dogs than in humans. (18) The postmortem length of the organ without fixation. (19) Guyton A. C. and Hall J. E., 1996*b*. (20) Ilett K. F., 1990. (21) The fasted gastric pH. In humans, postprandial gastric pH is initially higher (up to 7) owing to the buffering effect of food than the fasted gastric pH; then as gastric acid is secreted in response to eating, the pH gradually decreases to premeal values over a period of 60 to 90 min. In dogs, the initial buffering effect of food is not observed with more variability in postprandial pH (0.5 to 3–5, mean of 2.1). (22) pH in Wistar rats under fed condition. (23) Intestinal pH is consistently 1 unit higher in dogs than in humans at the same time of observation. (24) Chang R., 1981. (25) Measured as phenolphthalein produced from phenolphthalein β-glucuronidase in 1 hr at 38°C, and expressed as μg/g of moist tissue (Calabrese E. J., 1986). (26) Nanomoles of phenolphthalein-β-glucuronide deconjugated by bacterial β-glucuronidase present in proximal (distal) small intestine. (27) Numbers in parenthesis indicate mg microsomal protein content per g liver (Bäärnhielm C. *et al.*, 1986.

Table 13.2. Recommended Needle Size and Maximum Volume for Different Routes of Administration in Laboratory Animals[a]

	Weight	Needle size/maximum volume (ml)[b]				
		PO[c]	IV	IM	IP	SC
Mouse	20 g	1.0/0.5	25G/0.3	26G/0.05	26G/1	25G/0.5
Hamster	100 g	1.0/1	25G/0.5	25G/0.1	25G/3	25G/1
Rat[d]	250 g	2.0/2.5	25G/0.5[e]	25G/0.2	24G/5	24G/2
Guinea pig	600 g	2.0/4	24G/0.5	24G/0.3	24G/10	22G/3
Rabbit	4 kg	5.0/10	22G/5	23G/1	21G/50	21G/20
Cat	3 kg	—/10	22G/5	23G/1	21G/30	21G/20
Monkey	5 kg	—/10	22G/5	23G/1	21G/30	21G/20
Dog	10 kg	—/20	22G/10	21G/2	21G/100	20G/50

[a] Data taken from Fleckwell (1995), Iwarsson *et al.* (1994), Zwart (1993), and Sharp and LaRegina (1998).
[b] If compounds injected are irritants, much smaller volume should be used.
[c] Blunt cannula (oral gavage); firm restraint; vertical posture, pass tube along palate into esophagus (diameter of gavage (mm)/maximum volume).
[d] Intratracheal 40 µl, intranasal 100 µI, or subplantar 100 µl/foot (usually inject in only one foot).
[e] Single injection volume should not exceed 10% of the circulating blood volume and continuous 24-hr intravenous infusion should be less than 4 ml/kg body weight/hr.

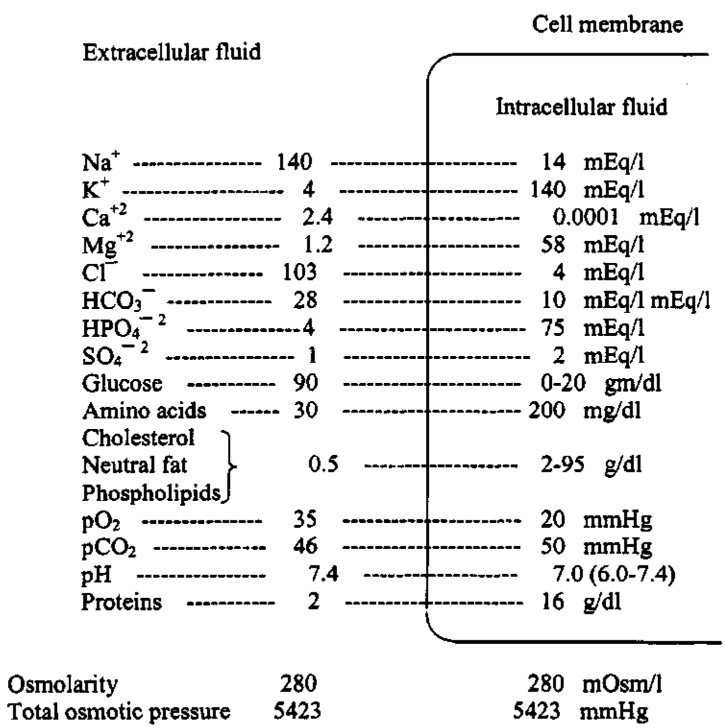

Figure 13.1. The chemical compositions of extracellular and intracellulaqr fluids and the physiological differences between them.

Table 13.3. Needle Sizes and the Corresponding Standard Wire Gauge[a]

Needle size (mm)[b]	0.35	0.45	0.55	0.7	0.9	1.25	1.65	2.10
Gauge (G)	28	26	24	22	20	18	16	14

[a] Data taken from Iwarsson et al. (1994).
[b] External diameter.

Table 13.4. Physiological Parameters of the Rat [a]

Basic biological parameters	
Gestation	21–23 days
Birth weight	5–6g
Life span	2.5–3.5years
Puberty	50 ± 10 days
Male body weight	450–520g [b]
Female body weight	250–300g [b]
Body temperature (rectal)	35.9–37.5°C
Body surface area	0.03–0.06cm^2
Food intake	50–60g/kg body weight/day
Water intake	100–120ml/kg body weight/day
GI transit time	12–24hr
Heart rate	330–480 beats/min
Cardiac output	10–80ml/min (mean of 50 ml/min)
Body fluids	
Total body water	167 ml [b]
Intracellular fluid	92.8 ml[b]
Extracellular fluid	74.2 ml[b]
Blood volume	57.5–69.9(mean of 64.1 ml/kg)
Plasma volume	36.3–45.3ml/kg (mean of 40.4 ml/kg)
Red blood cell volume	36.3 ± 1.0 mg/kg
Red blood cell (RBC) count	5–10 × 10^9/m1
White blood cell (WBC) count	3–17× 10^6/ml
Hemoglobin (HB)	110–190mg/ml
Hematocrit	0.35–0.57
Plasma albumin	29–59mg/ml
Cerebrospinal fluid (CSF) volume	250 ± 16 µl[c]
CSF formation rate	2.83 ± 0.18 µl/min (1.88 ± 0.17 µl/min[c])
CSF pressure	38 ± 4 mm Hg[c]
Urine volume	55 ml/kg body weight/day

[a] Data taken from Cocchetto and Bjornsson (1983) and Sharp and LaRegina (1998).
[b] Body weight may vary with stock or strain.
[c] 30-day-old rats.

Table 13.5. Injectable Anesthetics Suitable for Surgical or Light Anesthesia in Rats [a]

Type	Anesthesia time (min)	Anesthetic agent	Dose (mg/kg)[b]	Sleep time (min)
Surgical	≤5	Methohexital	10–15 IV	10
	≤5	Propofol	10 IV	10
	≤10	Thiopental	30 IP	15
	At least 20	Ketamine + xylazine	75–100 IP + 10 IP	120–240
Light	15	Pentobarbital	40–50 IV	120–240
	20–30	Ketamine + diazepam	75 IP + 5 IP	120
	20–30	Ketamine + midazolam	75 IP + 5 IP	120
	60	Chloral hydrate	300–400 IP	120–180
	—	Ketamine	100 IP	—
	—	Methohexitone	10 IV	—
	—	Thiopentone	30 IV	—
	—	Urethane	1000 IP	—

[a] Data taken from Sharp and LaRegina (1998).
[b] IP intraperitoneal injection; IV: intravenous injection.

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