

Rat and Dog Clinical Pathology Historical Control Data for Neonatal and Juvenile Toxicology Studies

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Introduction

The use of pharmaceutical and biotechnology products to treat pediatric patients requires that the conduct of neonatal and juvenile toxicology studies be considered before clinical trials are conducted. Rats and dogs are often selected as models for these non-clinical studies (FDA/EMA). Clinical pathology data has shown to be useful in understanding toxicity in these neonatal and juvenile toxicity studies.

Materials and Methods

The data presented in this poster was collected from groups of control animals from rat and dog neonatal and juvenile toxicology studies. Male and female rats CD[®] IGS rats (CrI:CD[SD]) were dosed by an appropriate method for at least 49 days commencing as young as Day 4 *post partum*. Male and female Beagle dogs were dosed by an appropriate method for at least 13 weeks commencing as young as Day 7 *post partum*. Group sizes for rats were at least 10/sex/group and for the dogs at least 6/sex/group. Mortality and signs of ill health or reaction to treatment were assessed at least once daily. Body weights were measured at least twice weekly throughout the preweaning and post weaning periods up to termination. Food consumption was assessed for the rats post weaning. Blood samples for laboratory investigations were performed on samples collected via the abdominal aorta or vena cava under isoflurane anesthesia for rats of ages up to Day 34 *post partum*. Blood samples were collected via the jugular vein from rats older than Day 34 *post partum* and from dogs of all ages. For tabulation purposes, the data for the rats was combined for assessments from Day 20 to 29, 30 to 39 and 40 to 49 *post partum*. For dogs, the data was combined to include assessments between Weeks 1 to 3, 4 to 6, 7 to 9, 10 to 12 and 13 to 15 *post partum*. Fasting of animals prior to blood sample collection for clinical biochemistry assessments typically can not be implemented prior to or soon after weaning for either species. Small sample volumes at the younger ages of the animals may require pooling of samples within litters and may also limit the number of assays performed during assessment.

Table 1: Historical Control Data 1998 - 2006 - Rat Sprague-Dawley (CD)

HEMATOLOGY PARAMETERS										
Parameter Units	MALES		Hemoglobin g/dL	Range g/dL	Hematocrit %	Range %	Reticulocytes 10 ³ /L	Range 10 ³ /L		
	RBC 10 ⁶ /uL	Range 10 ⁶ /uL								
Occasion/Age										
DAY 20 TO 29	4.7	4.5 - 4.8	9.4	9.1 - 9.7	29	28 - 30	847	796 - 898		
DAY 30 TO 39	6.0	5.9 - 6.1	12.6	12.4 - 12.8	40	39 - 41	554	527 - 580		
DAY 40 TO 49	6.4	6.3 - 6.5	13.5	13.3 - 13.7	41	41 - 42	474	451 - 497		
Parameter Units	FEMALES		Hemoglobin g/dL	Range g/dL	Hematocrit %	Range %	Reticulocytes 10 ³ /L	Range 10 ³ /L		
RBC 10 ⁶ /uL	Range 10 ⁶ /uL									
Occasion/Age										
DAY 20 TO 29	4.8	4.6 - 5.0	9.7	9.3 - 10.0	30	29 - 31	887	834 - 939		
DAY 30 TO 39	6.2	6.1 - 6.3	12.7	12.4 - 13.0	40	39 - 41	467	441 - 494		
DAY 40 TO 49	6.6	6.5 - 6.8	13.8	13.5 - 14.0	41	40 - 42	345	317 - 373		

Table 2: Historical Control Data 2001 - 2006 - Beagle Dog Pups

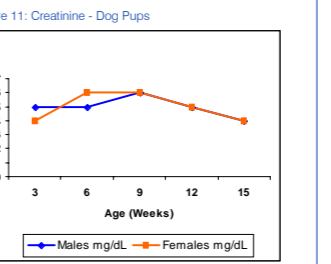
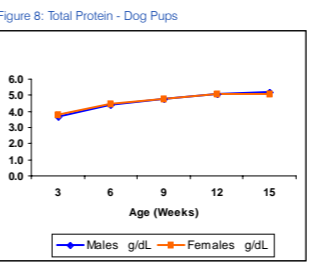
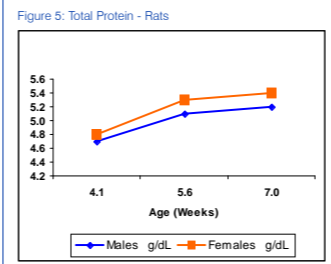
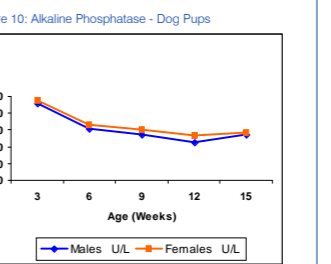
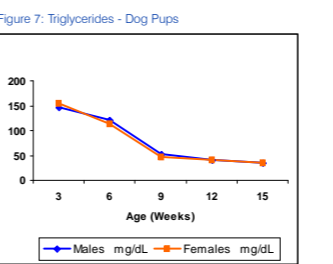
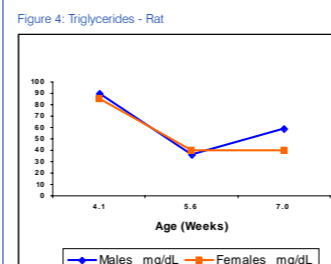
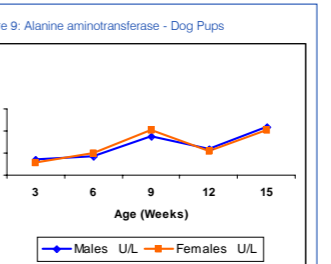
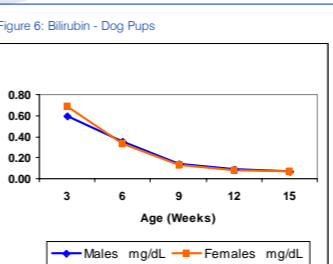
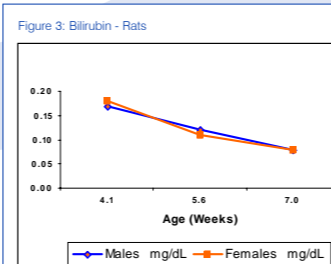
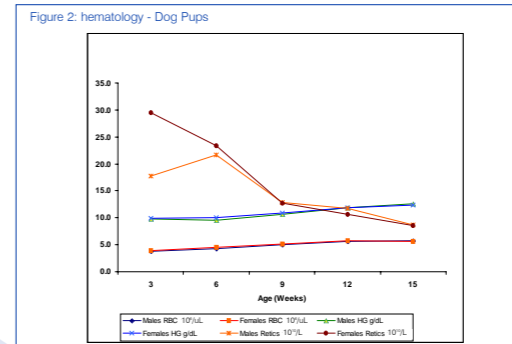
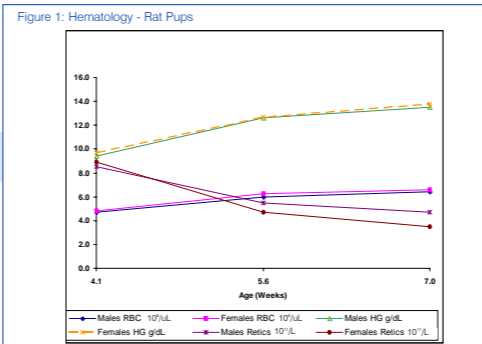
HEMATOLOGY PARAMETERS										
Parameter Units	MALES		Hemoglobin g/dL	Range g/dL	Hematocrit %	Range %	Reticulocytes 10 ³ /L	Range 10 ³ /L		
	RBC 10 ⁶ /uL	Range 10 ⁶ /uL								
Occasion/Age										
WEEK 1 TO 3	3.8	2.7 - 4.7	9.8	9.5 - 10.1	30	29 - 31	178	125 - 232		
WEEK 4 TO 6	4.3	4.1 - 4.4	9.6	9.3 - 9.9	31	30 - 32	216	131 - 355		
WEEK 7 TO 9	5.0	4.1 - 5.6	10.6	10.3 - 10.9	34	33 - 35	129	109 - 149		
WEEK 10 TO 12	5.6	5.5 - 5.7	11.9	11.5 - 12.3	37	35 - 38	117	88 - 147		
WEEK 13 TO 15	5.8	5.6 - 6.0	12.6	12.1 - 13.1	38	37 - 40	87	75 - 98		
Parameter Units	FEMALES		Hemoglobin g/dL	Range g/dL	Hematocrit %	Range %	Reticulocytes 10 ³ /L	Range 10 ³ /L		
RBC 10 ⁶ /uL	Range 10 ⁶ /uL									
Occasion/Age										
WEEK 1 TO 3	3.9	3.7 - 4.1	9.9	9.6 - 10.2	31	30 - 32	295	240 - 350		
WEEK 4 TO 6	4.5	4.3 - 4.6	10.0	9.7 - 10.3	32	31 - 33	234	214 - 255		
WEEK 7 TO 9	5.2	5.1 - 5.3	10.9	10.6 - 11.2	35	34 - 36	127	108 - 146		
WEEK 10 TO 12	5.8	5.6 - 6.0	11.9	11.5 - 12.3	37	36 - 38	107	89 - 125		
WEEK 13 TO 15	5.7	5.6 - 5.9	12.3	12.0 - 12.6	37	37 - 38	86	75 - 98		

Table 3: Historical Control Data 1998 - 2006 - Rat (CD:IGS)

CLINICAL BIOCHEMISTRY PARAMETERS														
Parameter Units	MALES		ALP U/L	Range U/L	TBL mg/dL	Range mg/dL	CHOL mg/dL	Range mg/dL	TRIG mg/dL	Range mg/dL	TPROT g/dL	Range g/dL	CREAT mg/dL	Range mg/dL
	ALT U/L	Range U/L												
Occasion/Age														
DAY 20 TO 29	43	39 - 47	341	315 - 367	0.17	0.14 - 0.20	77	70 - 83	90	70 - 109	4.7	4.6 - 4.8	0.4	0.33 - 0.41
DAY 30 TO 39	34	32 - 36	283	260 - 306	0.12	0.11 - 0.13	61	56 - 66	36	31 - 42	5.1	5.0 - 5.2	0.3	0.29 - 0.35
DAY 40 TO 49	38	35 - 40	315	294 - 336	0.08	0.07 - 0.9	61	59 - 64	39	30 - 68	5.2	5.1 - 5.39	0.3	0.23 - 0.29
Parameter Units	FEMALES		ALP U/L	Range U/L	TBL mg/dL	Range mg/dL	CHOL mg/dL	Range mg/dL	TRIG mg/dL	Range mg/dL	TPROT g/dL	Range g/dL	CREAT mg/dL	Range mg/dL
ALT U/L	Range U/L													
Occasion/Age														
DAY 20 TO 29	40	36 - 43	333	304 - 361	0.18	0.13 - 0.23	80	74 - 86	85	62 - 108	4.8	4.7 - 4.9	0.4	0.36 - 0.44
DAY 30 TO 39	28	27 - 30	340	222 - 297	0.11	0.10 - 0.12	70	63 - 77	40	35 - 46	5.3	5.2 - 5.4	0.3	0.27 - 0.33
DAY 40 TO 49	32	29 - 34	218	202 - 255	0.08	0.07 - 0.09	67	63 - 111	40	34 - 46	5.4	5.3 - 5.5	0.3	0.27 - 0.33

Table 4: Historical Control Data 2001 - 2006 - Beagle Dogs

CLINICAL BIOCHEMISTRY PARAMETERS														
Parameter Units	MALES		ALP U/L	Range U/L	TBL mg/dL	Range mg/dL	CHOL mg/dL	Range mg/dL	TRIG mg/dL	Range mg/dL	TPROT g/dL	Range g/dL	CREAT mg/dL	Range mg/dL
	ALT U/L	Range U/L												
Occasion/Age														
WEEK 1 TO 3	14	11 - 17	330	195 - 264	0.60	0.49 - 0.71	234	209 - 239	147	130 - 164	3.7	3.6 - 3.8	0.5	0.48 - 0.52
WEEK 4 TO 6	18	15 - 20	154	139 - 168	0.35	0.25 - 0.45	241	227 - 255	122	105 - 140	4.4	4.3 - 4.5	0.5	0.39 - 0.61
WEEK 7 TO 9	35	27 - 43	136	126 - 146	0.14	0.08 - 0.20	164	150 - 178	52	41 - 63	4.8	4.7 - 4.9	0.6	0.50 - 0.70
WEEK 10 TO 12	24	19 - 28	113	91 - 136	0.08	0.07 - 0.11	212	187 - 238	42	32 - 51	5.1	4.9 - 5.3	0.5	0.47 - 0.63
WEEK 13 TO 15	44	36 - 52	137	129 - 145	0.07	0.06 - 0.08	182	169 - 194	35	33 - 37	5.2	5.1 - 5.3	0.4	0.36 - 0.44
Parameter Units	FEMALES		ALP U/L	Range U/L	TBL mg/dL	Range mg/dL	CHOL mg/dL	Range mg/dL	TRIG mg/dL	Range mg/dL	TPROT g/dL	Range g/dL	CREAT mg/dL	Range mg/dL
ALT U/L	Range U/L													
Occasion/Age														
WEEK 1 TO 3	12	9 - 15	337	206 - 268	0.69	0.51 - 0.87	231	214 - 249	156	127 - 184	3.8	3.7 - 3.9	0.3	0.37 - 0.43
WEEK 4 TO 6	20	15 - 24	165	150 - 177	0.33	0.23 - 0.43	228	217 - 239	114	93 - 135	4.5	4.4 - 4.6	0.6	0.48 - 0.72
WEEK 7 TO 9	41	33 - 48	151	139 - 163	0.13	0.08 - 0.18	161	148 - 174	48	41 - 54	4.8	4.7 - 4.9	0.6	0.50 - 0.70
WEEK 10 TO 12	22	19 - 28	134	85 - 153	0.08	0.07 - 0.09	203	191 - 245	40	35 - 45	5.0	5.0 - 5.2	0.5	0.45 - 0.55
WEEK 13 TO 15	41	37 - 44	141	132 - 149	0.07	0.06 - 0.08	175	167 - 184	36	33 - 38	5.1	5.0 - 5.2	0.4	0.37 - 0.43



Results

Compilation of control data by age for rat and dog show changes across time for some parameters are generally similar in both species. Hematological parameters having changes associated with an increase in age include increases in erythrocyte counts, hemoglobin and hematocrit values and decreases in reticulocytes for both species. There were no differences in any of the hematological parameters that were considered to be attributed to sex.

For clinical biochemistry parameters, bilirubin and triglyceride values tend to decrease with age and protein levels tend to increase with age for both species. Cholesterol values decrease for female rats at all intervals up to Day 49 *post partum* and for male rats up to Day 39 *post partum*. For Beagle dogs, cholesterol values tend to decrease up to the end of Week 9. Alanine aminotransferase levels increase up to the end of Week 9 and alkaline phosphatase levels decrease up to the end of Week 12 for dogs but are generally not affected for rats. Again, there are no differences in any of the clinical biochemistry parameters that were considered to be attributed to sex.

Conclusion

The changes in some clinical pathology parameters with advancing age illustrate the necessity of having adequate historical control data when evaluating clinical pathology data for neonatal and juvenile toxicology studies.

Acknowledgements

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