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Anesthesia of Pediatric Small Animal Patients

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Introduction

The practicing veterinarian is rarely called on to provide general anesthesia to pups or kittens during the first 2 weeks of life as little demand exists for complex surgical services or diagnostic procedures in this age group. Cosmetic procedures, such as tail docking and dewclaw removal, are performed on very young pups, but supplemental analgesia is often withheld due to concerns for anesthetic-induced complications. Anesthesia and analgesia can be easily provided to pups and kittens, as long as certain considerations are kept in mind. The goal of this chapter is to provide a brief overview of the physiology of the neonatal and pediatric small animal patient, and to discuss recommendations for their safe anesthesia.

Defining the Neonatal and Pediatric Periods

In humans, the neonatal period is defined as ⩽4 weeks of age, after which the pediatric period begins [1]. By the time the pediatric human infant is 16 weeks of age, circulatory and ventilatory adaptations to life outside the uterus are largely complete. Over the next 1 to 1.5 years, the human infant gradually transforms into a miniature adult as far as the conduct of anesthesia is concerned [2]. During this time, skeletal muscle mass and hepatic enzyme systems continue to develop, renal function matures, composition of body fluid compartments approach adult values, and thermoregulation matures to a more adult state.

For small animals, definitions of the neonatal and pediatric periods vary considerably. Cornick-Seahorn [3] defines the neonatal period as ⩽12 weeks of age, while Grundy [4] defines it as the 4 weeks from birth to weaning. If an analogy is made to humans, the first 2 weeks of extra-uterine life in dogs and cats can be defined as the neonatal period. The next 3 to 8 weeks can be defined as the pediatric period in small animals, as similar maturation of organ function that occurs in humans also occurs during this time. Puppies and kittens older than 8 weeks can be considered miniature adults from a physiologic and pharmacokinetic standpoint, a position that is clinically supported by Faggella and Aronsohn's reports of successfully anesthetizing 6 to 14 week old puppies and kittens for an early spay and neuter program using adult doses (as mg/bodyweight) of injectable anesthetics [5,6].

Respiratory Considerations

The physiology of the small animal neonatal and pediatric patient was recently reviewed by Hosgood [7] and Grundy [4]. Young animals consume oxygen at a rate 2-3 times greater than adults, but have tidal volumes similar to adults (12-15 ml/kg). The ratio of minute volume to functional residual capacity (FRC) is high. Thus, resting respiratory rate must be 2-3 times greater to provide the minute ventilation necessary to meet oxygen demand. The resulting high alveolar ventilation will increase exchange of gases within the lungs, leading to faster induction and recovery from inhalant anesthetics. Because of this, inhalant overpressure (a technique in which a high inhaled concentration of an inhalant anesthetic is delivered by mask or chamber to induce anesthesia) will tend to rapidly induce anesthesia in neonates and place them at risk for anesthetic overdose. Hypoxemia and anesthetic overdose may present as bradycardia in neonates (see below).

Respiratory control is immature in neonates and ventilatory responses to moderate hypoxia differ significantly compared to adults. Respiratory control mechanisms develop prior to birth, but require postnatal maturation. The combination of high metabolic oxygen requirement and immature carotid body chemoreceptors can lead to hypoxemia. Response to hypoxemia is characterized by transient hyperpnea followed by return of ventilation toward or below the control level, and even apnea.

The rib cage of puppies and kittens is more pliable than adults, resulting in greater chest wall compliance and overlap of airway closing volume with tidal volume. Tracheobronchial airways are smaller, less rigid, and alveoli are smaller. Closing volume is the lung volume at which alveoli close, which causes shunting of blood past closed alveoli, and increases

pulmonary shunt. Partial or complete airway obstruction from any cause can result in rapid oxygen desaturation.

Risk of airway obstruction can be greater in neonatal animals than in adults as the nares tend to be small and the tongue takes up a relatively larger portion of the oral and pharyngeal cavity. Intubation may be difficult, due to poor visualization of the larynx and reduced interior diameter of the laryngeal cartilage. Even if it is possible to place a small diameter tube within the trachea, resistance to flow increases drastically as tube radius decreases ($R \approx 1/r4$). Thus, for routine procedures in very young or very small animals, extending the head and using a snug-fitting face mask may be better than trying to place small endotracheal tubes fabricated from urinary or red rubber feeding catheters.

Oxygen therapy has the potential to significantly raise neonatal PaO_2. Growing evidence from both animal and human studies, however, suggests 100 percent oxygen may have adverse effects on neonatal breathing physiology and cerebral circulation due to free radical formation. Room air is seemingly as effective as 100 percent oxygen for neonatal resuscitation, with reduced neonatal mortality and no evidence of harm reported in human infants resuscitated with room air [8]. Oxygen should still be available during resuscitation or general anesthesia, however, especially for compromised neonates, or in those situations where there is evidence of oxygen desaturation.

Circulatory Considerations

Following birth, the neonatal circulatory system is characterized as low pressure, low volume, and low peripheral resistance. The ability of the neonatal cardiovascular system to respond to stress early in the neonatal period is limited by low myocardial contractility and the immature sympathetic nervous system. Atropine has minimal effect on heart rate prior to 14 days of age in puppies, and vagal stimulation has no effect on heart rate prior to 11 days of age in kittens, implying lack of full cardiac autonomic development [9,10]. It is important to realize that bradycardia in the neonate is not vagally mediated and may be indicative of hypoxemia.

The baroreceptor reflex is responsible for the tachycardia that occurs in response to hypotension. In contrast to changes in heart rate due to autonomic stimulation, vasomotor tone, as the basis of the baroreceptor reflex, is functional by 4 days of age. However, the baroreceptor reflex is more depressed in the neonate than the adult at similar levels of anesthesia.

Resting neonatal cardiac output is close to maximal, with limited reserve, and is dependent on heart rate (see Table 1 and Table 2). In neonates because of their higher O_2 consumption (where $DO_2 = CO^* CaO_2$), resting cardiac output is much higher relative to body weight than in adults. Any slowing of heart rate reduces cardiac output and conversely, any increase in cardiac output must be accompanied by an increase in heart rate (where C = HR*SV). Ventricular compliance is reduced as well, limiting the ability of the neonate to increase stroke volume in response to IV fluid volume loading. In addition, the neonate's ability to compensate for hemorrhage is poor compared with adults.

Table 1. Mean arterial pressure and heart rate for awake mongrel puppies

Age (weeks)	Mean Arterial Pressure (mmHg)	Heart Rate (beats/min)
4	49	173
8	55	150
12	62	130
16	74	120
20	75	110
24	83	95
28	92	85
36	94	71

Adapted from Magrini F., [11].

Although regional blood flow to individual organs can be adjusted by autoregulation in neonatal and adult animals, the blood pressure limits of effective neonatal autoregulation are not well-defined. Blood pressure is monitored as an indirect indicator of adequacy of cardiac output and organ perfusion during anesthesia (where mean arterial blood pressure (MAP) = CO * Systemic Vascular Resistance). In adults, mean arterial pressure is maintained $\geq$70 mmHg to maintain autoregulation of tissue and organ perfusion. Neonatal and pediatric blood pressures, however, are substantially lower than for adults due to the reasons given above. Guidelines for determining adequacy of perfusion during anesthesia of neonatal

and pediatric patients must be age-adjusted downward from those expected of adults.

Table 2. Systolic blood pressure and heart rate for awake Beagle puppies			
Age (weeks)	**Weight (kg)**	**Systolic Blood Pressure (mmHg)**	**Heart Rate (beats/min)**
0-1	0.54	61	204
1-4	0.95	82	190
4-8	1.96	112	196
8-12	3.32	132	182
12-16	4.92	131	158
16-20	6.62	136	153
20-24	8.02	136	135
24-28	8.80	136	123
Adapted from Adelman RD, Wright J., [12].			

One way to minimize surgical blood loss in neonatal and pediatric patients is through control of blood pressure by anesthetics. Volatile anesthetics reduce blood pressure by 20 to 30%. Both isoflurane and sevoflurane are used to anesthetize neonatal and pediatric small animals and both produce similar dose-dependent reductions in blood pressure. Hypotension in human neonates is defined as blood pressure below the fifth percentile of the gestational- and postnatal-age-dependent blood pressure norms [13]. Although one should strive for age-adjusted normotension in anesthetized neonatal and pediatric patients, arterial pressures between 50 to 60 mmHg have been shown to be without deleterious effects in anesthetized full-term human neonates with awake blood pressures between 60 and 70 mmHg [1]. In addition, there is evidence in neonatal lambs that although cardiac output, and thus oxygen delivery, decreases during isoflurane anesthesia ($\leqslant$1.0 MAC), organ oxygen requirement decreases in a parallel fashion with no apparent diversion of cardiac output from non-vital (i.e., muscle) to vital organs (i.e., brain, heart) [14].

Hematologic Considerations

Hematologic parameters for growing puppies and kittens are summarized by Grundy [4]. Hemoglobin levels decline following birth due to lower erthyrocyte production, shorter erythrocyte life span, and hemodilution by an expanding blood volume. More specifically, hemoglobin levels are highest at birth, fall to near 8.5 g/dL by 2 - 4 weeks of age and rise to near adult levels by 30 weeks of age. Relatively small volumes of blood loss may therefore result in anemia, especially in animals between 2 and 8 weeks of age, as hematopoesis does not begin until after 4 weeks of age [15].

Neonatal puppies and kittens have a high percentage of fetal hemoglobin (70 - 80%), which has greater oxygen affinity than adult hemoglobin. Oxyhemoglobin affinity decreases in neonatal dogs 15 days following birth due to increasing levels of 2,3-diphosphoglycerate (2,3-DPG); in contrast, neonatal kittens, like adult cats, show low sensitivity to 2,3-DPG and the subsequent decrease in oxyhemoglobin binding affinity noted after birth is attributed to a fall in red cell trans-membrane pH difference [16].

Metabolic and Pharmacological Considerations

Drug disposition and pharmacokinetics will be different in neonates compared to adults because of lower plasma albumin, larger percentage of total body water, lower amount of body fat, greater distribution of cardiac output to vessel-rich organs, and reduced hepatic and renal function. Albumin levels in puppies younger than 4 weeks are lower than in adults, but attain adult levels by 8 weeks of age [17]. Thus in the first 4 to 8 weeks of life, neonates may show greater sensitivity to highly protein bound drugs (e.g., thiobarbiturates) administered IV due to reduced albumin binding, and an apparent resistance to non-protein bound drugs (e.g., muscle relaxants) due to a larger volume of distribution. Repeated doses of drugs requiring redistribution to muscle and fat for termination of action will generally result in prolonged effect in this age group.

Hepatic P450-dependent microsomal oxidation, often followed by glucuronide conjugation, is the principal metabolic pathway for a number of lipid-soluble drugs, including many anesthetics. Hepatic enzyme systems in puppies and kittens are immature at birth, but rapidly approach and exceed adult levels. Cytochrome P450 activity rises to 85% of adult levels between 4 to 6 weeks of age and reaches adult levels by 4 to 5 months of age; in contrast, glucose-6-phosphatase, p-nitrophenol glucaronyl transferase, and bilirubin gluraronyl transferase rise to 188%, 105%, and 123%, respectively, of

adult levels between 4 to 6 weeks of age [18]. Cumulation of hepatically metabolized drugs is therefore likely to occur in neonatal small animal patients <4 weeks of age and redosing should be based on effect in the absence of therapeutic drug monitoring. Cumulation will be less problematic in pediatric puppies and kittens >4 weeks of age. In human neonates, it is currently recommended that drugs primarily metabolized by the liver be administered with extreme care until the age of 8 weeks, after which a general guideline based on body weight can be used [19]. Based on the reports of Faggella and Arohnson [5,6] concerning anesthetic management of 6 to 14 week old puppies and kittens, dose guidelines for injectable anesthetic drugs used in adults can be safely used in neonatal animals after 6 weeks of age without evidence of prolonged recovery, implying adequate metabolism and clearance. Similar anesthetic recommendations for this age group have been made by Hosgood [7].

Immaturity of the blood-brain barrier has been suggested as a reason why neonates are more sensitive to the effects of anesthetics, particularly morphine [20], however, this may not be true. Luks et al., [21] examined changes in the pharmacokinetics of morphine and fentanyl in Beagle puppies as they matured over 1 to 35 days of age. The concentration of morphine needed to depress ventilation in the first 4 weeks of life increased markedly (80-fold) while analgesic sensitivity decreased slightly (3.4-fold); for fentanyl maturational decreases in sensitivity to the ventilatory (4.1-fold) and analgesic (3.9-fold) depressant effects were similar in this age group. Although sensitivity to opioids decreased with age, the rate of equilibrium between plasma concentration and effect did not vary with age. Assuming both analgesic and ventilatory depressant effects of opioids reflect their brain concentrations, the findings of Luks and coworkers [21] suggest neonatal sensitivity to opioids is mainly due to factors that influence plasma concentration as a function of time (e.g., uptake, distribution, elimination) rather than immaturity of the blood-brain barrier.

Renal Considerations

The neonatal dog kidney is morphologically and functionally immature at birth; glomerular filtration matures between 2 and 3 weeks of age, while tubular secretion matures between 4 and 8 weeks of age. Creatinine and blood urea nitrogen levels are lower than in the adult. Proximal tubule natriuresis is greater in the neonate in response to saline expansion than in the adult but overall renal Na+ excretion is less due to enhanced fractional Na+ reabsorption in the neonatal distal nephron, particularly in Henle's Loop [22]. The neonatal canine kidney is characterized by low glomerular filtration rate, renal plasma flow, filtration fraction, depressed absorption of amino acids, and low concentrating ability [4]. Increases in glomerular filtration rate and renal plasma flow occur in parallel, but not necessarily in phase with structural development [23]. Autoregulation of renal blood flow occurs but is not influenced by inhibition of angiotensin [24]. Similar information for kittens is lacking. Urine protein and glucose levels are higher in puppies and kittens than in adults, while urine specific gravity is lower [7].

Thermoregulation

Hypothermia is likely to develop during anesthesia of both neonates and pediatric small animals due to their large surface area-to-volume ratio, as well as the depressant effects of anesthetics on thermoregulation and reduced overall voluntary movement and shivering muscular activity. Neonates are poikilothermic, but possess well developed behavioral heat-seaking responses which permit them to maintain stable body temperature provided exogenous heat sources are available. At weaning, puppy and kitten rectal temperatures are similar to adults. Hypothermia results in bradycardia, decreased cardiac output and hypotension, and prolongs drug elimination and recovery times. Conduction, radiation, convection, and evaporation can all contribute to intraoperative heat loss.

Anesthetic Recommendations

1. An accurate weight is required prior to administering sedative or anesthetic agents to neonatal or pediatric patients.

2. Preoperative fasting of neonatal and pediatric small animals is generally unnecessary prior to anesthesia and should not exceed 1 to 2 hours. Although normal blood glucose levels can be maintained in healthy, fasted neonatal puppies and kittens through hepatic gluconeogenesis [25], hepatic glycogen stores are minimal and rapidly decline during fasting. A microhematocrit tube filled from a percutaneously placed needle hub can be used together with a commercial glucometer to track blood glucose status with minimal blood loss. Excessive glucose administration should be avoided, as it will tend to promote osmotic diuresis and dehydration; both half-strength lactated Ringer's with 2.5% dextrose and 0.45% sodium chloride with 2.5% dextrose are iso-osmotic and available commercially.

3. An anticholinergic agent (i.e., atropine or glycopyrolate should be routinely administered to maintain heart rate prior to general anesthesia or administration of opioids, but may have little or no effect in puppies or kittens less than 14 days old (see above).

4. Sedation is rarely needed in neonates, although it may be necessary for pediatric pups and kittens in rare cases. Sedative and tranquilizing drugs, such as acepromazine or the benzodiazepines, require hepatic metabolism but can be used cautiously at low doses, if necessary. Hosgood [7] provides an extensive list of anesthetic and analgesic drugs for pediatric puppies and kittens. It is important to realize that duration of effect may be prolonged in some individuals

and redosing should be based on evaluation of effect, rather than time.

The α-2 agonists can cause anticholinergic-responsive bradycardia. In addition, α-2 agonists increase aortic blood pressures by increasing systemic vascular resistance, which further depresses cardiac output in neonates unable to increase stroke volume in response to an increased afterload. These agents can not be recommended for use in puppiess or kittens < 8 weeks old.

Opioids are excellent analgesics and are generally well tolerated by pediatric patients. Opioids may cause sinus bradycardia and second degree heart block and should be administered with anticholinergics. When administered to puppies less than 4 weeks of age, respiratory depression is more likely with morphine than with fentanyl, and may occur before morphine produces analgesia [21]. Opioids undergo hepatic metabolism; prolonged CNS depression is usually not seen in pediatric patients and either full or partial mu-receptor antagonists can be administered, if necessary, to reverse their effects.

5. Mask induction with inhaled anesthetics is my preferred choice for general anesthesia of neonatal puppies and kittens. As previously discussed, induction (as well as changes in depth and recovery) will be faster in neonates and pediatric patients due to more rapid alveolar gas exchange, and requires close monitoring. Neonates can be easily restrained for mask or chamber induction, and pediatric patients can be sedated, if needed, with an opioid (pups) or a low dose of ketamine (kittens), both of which may allow maintenance with lower levels of inhalant. The author does not recommend use of injectable induction agents (i.e., thiobarbiturates, ketamine combinations, zolazepam /tiletamine, propofol) on small animals < 4 weeks of age. Animals ⩾ 6 weeks of age can be successfully anesthetized using adult doses as mg/bodyweight [see 5-7].

6. Intravenous or intraosseous fluids should be administered at 4 to 10 ml/kg/hr during anesthesia to allow for insensible water loss, limited blood loss, and to prevent hypotension. An in-line graduated cylinder (e.g., Buretrol^{tm}) and minidrip infusion set (60 drips/ml), or syringe pump, can be used to quantitate fluid delivery.

7. Animals should be insulated from cold surfaces, exposure of abdominal viscera should be minimized, and anesthesia time should be minimized. Cutaneous heat loss represents 74% of total heat flux in an anesthetized swine model [see 26]; simply insulating the puppy or kitten during anesthesia will help reduce perioperative hypothermia. Heated air blankets and circulating water blankets are ideal for thermal management when combined with "dry" surgical site preparation and minimal surgery time. Bubble wrap or clear plastic food wrap can also be used to insulate small animals. Infra-red heat lamps, containers or gloves filled with hot water, or microwaved rice bags must be used with caution, as cutaneous burns can result.

8. Animals < 5 kg will benefit from use of non-rebreathing anesthetic circuits (e.g., Mapleson D, E, and F circuits) at a fresh gas flow rate of 200 ml/kg/min. These non-rebreathing circuits do not have valves, offer lower respiratory resistance and respiratory work, and allow more rapid control in anesthetic level than rebreathing circuits. On the other hand, breathing dry room temperature anesthetic gases increases respiratory heat loss, from approximately 10% in the awake patient, to 15% in anesthetized patients [27]. End-tidal carbon dioxide ($ETCO_2$) will be falsely low with non-rebreathing circuits due to low patient tidal volume relative to the high fresh gas flows used.

9. Local anesthesia should be considered for awake minor surgical procedures. The afferent sensory system in pups and kittens is well differentiated at birth. From birth, neonatal small animals exhibit withdrawal reflexes and vocalize in response to cutaneous pin pricks and sustained noxious stimuli [28]. Although somewhat controversial, use of subcutaneous infiltration or blebbing with 0.5 to 1.0% lidocaine prior to dewclaw removal, or ring block, or caudal epidural block prior to tail docking may provide analgesia and prevent nociceptive windup with little additional cost in time or supplies; lidocaine transdermal patches or EMLA cream (Eutectic Mixture of Local Anesthetics, a combination of lidocaine and prilocaine) may also be effective.

   Methemoglobinemia following topical use of local anesthetics has been well-described and is associated with benzocaine, prilocaine, procaine, and lidocaine. Development of methemoglobinemia is dependent on dose, and is more common in neonates due to decreased resistance of fetal hemoglobin to oxidative stress and immature erythrocyte methemoglobin reductase activity [29].

   Alkalinizing local anesthetics such as lidocaine or bupivacaine may reduce the pain that occurs when these drugs are injected into tissue, however, adding sodium bicarbonate is controversial. The pH of commercially available local anesthetics ranges from 3.9 to 6.5; the addition of epinephrine to commercial solutions further reduces pH. The addition of sodium bicarbonate has been proposed to raise the pH closer to the pKa in order to increase the amount of uncharged lipid-soluble active base of local anesthetic. However, clinically used local anesthetics cannot be

alkalinized beyond a pH of 6.05 to 8 before precipitation occurs; the increase in active base in this pH range will only be about 10% [30]. In rats, addition of sodium bicarbonate to 1% commercial lidocaine without epinephrine decreased the degree and duration of block, but addition of sodium bicarbonate to solutions with epinephrine hastened onset of blockade without influencing degree or duration [31]. In horses, carbonated 2% lidocaine did not differ from 2% lidocaine in onset time, duration, or degree of sensory blockade for caudal epidural block [32]. In a double-blind study in human volunteers, pain scores were lower with buffered lidocaine-epinephrine, but not statistically different from lidocaine with freshly added epinephrine [33].

Conclusions

Which anesthetic agent or technique is best for your neonatal and pediatric patients? The answer depends on your knowledge, skills, and experience as well as the surgical needs of the patient. Rarely is a situation encountered where a single agent or technique is exclusively indicated. On the other hand, anesthetic agents and techniques do not create identical effects. Careful and considered thought should go into the selection of the best anesthetic for your situation, the patient, and the anticipated procedure.

Additional Reading

1. Grandy JL, Dunlop CI. Anesthesia of pups and kittens. J Am Vet Med Assoc 1991; 198:1244-1249.

2. Meyer RE. Anesthesia for neonatal and geriatric patients. In: Short, CE, ed. Principles and Practice of Veterinary Anesthesia. Baltimore, Williams and Wilkins, 1987; 330-337.

3. Rankin DC. Neonatal Anesthesia. In: Greene SA, ed. Veterinary Anesthesia and Pain Management Secrets. Philadelphia, Hanley and Belfus, 2002; 211-213.

4. Thurmon JC, Tranquilli WJ, Benson GJ. Neonatal and geriatric anesthesia. In: Thurmon JC, Tranquilli WJ, Benson, GJ, eds. Lumb and Jones' Veterinary Anesthesia, 3rd ed. Philadelphia, Williams and Wilkins, 1996; 844-845.

References

1. Berry FA, Castro BA. Neonatal anesthesia. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical Anesthesia, 5th ed. Philadelphia, Lippincott Williams and Wilkins, 2006; 1181-1204.

2. Rice LJ, Cravero J. Pediatric Anesthesia. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical Anesthesia, 3rd. ed. Philadelphia, Lippincott-Raven, 1997; 1115-1124.

3. Cornick-Seahorn JL. Veterinary Anesthesia. Boston, Butterworth-Heinemann, 2001; 299-300.

4. Grundy SA. Clinically Relevant Physiology of the Neonate. Vet Clin Small Anim 2006; 36:443-459.

5. Faggella AM, Aronsohn MG. Anesthetic techniques for neutering 6- to 14-week-old kittens. J Am Vet Med Assoc 1993; 202:56-62; Comments J Am Vet Med Assoc 1993; 202:1040-1041.

6. Faggella AM, Aronsohn MG. Evaluation of anesthetic protocols for neutering 6- to 14-week-old pups. J Am Vet Med Assoc 1994; 205:308-314.

7. Hosgood G. Anesthesia and surgical considerations. In: Hoskins, JD, ed. Veterinary Pediatrics, 3rd ed. Philadelphia, W.B. Saunders, 2001; 525-547.

8. Tan A, Schulze A, O'Donnell CP, et al., Air versus oxygen for resuscitation of infants at birth. Coch Database Sys Rev 2005: 18:CD002273.

9. Mace SE, Levy MN. Neural control of heart rate: a comparison between puppies and adult animals. Pediatr Res 1983; 17:491-495.

10. Fox MW. Developmental physiology and behavior. In: Fox MW, Himwich WA, eds. Canine pediatrics. Springfield (MO), Charles C. Thomas, 1966; 22-25.

11. Magrini F. Haemodynamic determinants of the arterial blood pressure rise during growth in conscious puppies. Cardiovasc Res 1978; 12:422-428.

12. Adelman RD, Wright J. Systolic blood pressure and heart rate in the growing beagle puppy. Dev Pharmacol Ther 1985; 8:396-401.

13. Seri I. Management of hypotension and low systemic blood flow in the very low birth weight neonate during the first postnatal week. J Perinatol. 2006; 26 Suppl 1:S8-13; discussion S22-23.

14. Brett CM, Teitel DF, Heymann MA, et al., The cardiovascular effects of isoflurane in lambs. Anesthesiol 1987; 67: 60-65.

15. Mueggler PA, Black JA, Carpenter S, et al., Postnatal regulation of oxygen delivery: control of erythropoiesis following birth in dogs. Respir Physiol 1981; 43:189-196.

16. Dhindsa DS, Metcalfe J. Post-natal changes in oxygen affinity and the concentration of 2,3-diphosphoglycerate in cat blood. Resp Physiol 1974; 21:37-46.

17. Center SA, Hornbuckle WE, Hoskins JD. The liver and pancreas. In: Hoskins JD, ed. Veterinary Pediatrics, 2nd ed. Philadelphia, W.B. Saunders, 1995; 189.

18. Tavoloni N. Postnatal changes in hepatic microsomal enzyme activities in the puppy. Biol Neonate 1985; 47:305-316.

19. Bartelink IH, Rademaker CM, Schobben AF, et al., Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet 2006; 45:1077-1097.

20. Kupferberg HJ, Way EL. Pharmacologic basis for the increased sensitivity of the newborn rat to morphine. J Pharmacol Exp Ther 1963; 141: 105-112.

21. Luks AM, Zwass MS, Brown RC, et al., Opioid-induced analgesia in neonatal dogs: pharmacodynamic differences between morphine and fentanyl. J Pharmacol Exp Ther 1998; 284:136-141.

22. Kleinman LI, Banks RO. Segmental nephron sodium and potassium reabsorption in newborn and adult dogs during saline expansion. Proc Soc Exp Biol Med 1983; 173:231-237.

23. Kleinman LI, Lubbe RJ. Factors affecting the maturation of glomerular filtration rate and renal plasma flow in the new-born dog. J Physiol 1972: 223:395-409.

24. Jose PA, Slotkoff LM, Montgomery S, et al., Autoregulation of renal blood flow in the puppy. Am J Physiol 1975; 229:983-988.

25. Kliegman RM, Miettinen EL, Morton SK. Hepatic and cerebral energy metabolism after neonatal canine alimentation. Pediatr Res 1983; 17:285-291.

26. English MJ, Papenberg R, Farias E, et al., Heat loss in an experimental animal model. J Trauma 1991; 31:36-38.

27. Davis PD, Kenny GNC. Heat capacity and latent heat. In: Davis PD, Kenny GNC, eds. Basic physics and measurement in anaesthesia, 5th ed. Edinburgh, Butterworth-Heinemann, 2003; 103; 107-114.

28. Robinson EP. Anesthesia of pediatric patients. Comp Cont Ed Vet Pract 1983; 5:1004-1011.

29. Stoelting RK, Hillier SC. Pharmacology and physiology in anesthetic practice, 4th ed. Philadelphia, Lippincott Williams and Wilkins 2006; 193-194.

30. Ikuta PT, Raza SM, Durrani Z, et al., pH adjustment schedule for the amide local anesthetics. Reg Anesth 1989; 14:229-235.

31. Sinnott CJ, Garfield JM, Thalhammer JG, et al., Addition of sodium bicarbonate to lidocaine decreases the duration of peripheral nerve block in the rat. Anesthesiol 2000; 93:1045-1052.

32. Schelling CG, Klein LV. Comparison of carbonated lidocaine and lidocaine hydrochloride for caudal epidural anesthesia in horses. Am J Vet Res. 1985; 46:1375-1377.

33. Burns CA, Ferris G, Feng C., et al., Decreasing the pain of local anesthesia: a prospective, double-blind comparison of buffered, premixed 1% lidocaine with epinephrine versus 1% lidocaine freshly mixed with epinephrine. J Am Acad Dermatol. 2006; 54: 128-131.