Dose effect and benefits of glycopyrrolate in the treatment of bradycardia in anesthetized dogs

Doris H. Dyson, Rick James-Davies

Abstract — This study evaluated the effectiveness of glycopyrrolate (0.005 or 0.01 mg/kg body weight (BW)) in anesthetized dogs ($n = 40$) for reversal of bradycardia (< 65 beats/min). Following random intravenous (IV) treatment, heart rate was determined at 5 min and, if it was ≤ 70 beats/min, the lower dose was repeated. A 2-way analysis of variance considered dose and animal size (≤ 10 kg, > 10 kg) effects ($P < 0.05$). Glycopyrrolate produced a significant increase in heart rate and infrequent tachycardia (≤ 150 beats/min), which was not dose-related. The size of the dog produced a significant effect on baseline heart rate (higher in small), rate following the first dose (lower in small), and requirement for retreatment (47% in small, 13% in large). In a separate group of anesthetized dogs ($n = 20$), the blood pressure effect of glycopyrrolate (0.01 mg/kg BW, IV) treatment of bradycardia (65–85 beats/min, weight-adjusted) was studied. A significant increase in systolic, diastolic, and mean blood pressure was produced. In conclusion, the effective dose of glycopyrrolate treatment is size-related and produces a beneficial effect on blood pressure.

Résumé — Effets favorables du glycopyrrolate en relation avec la dose dans le traitement de la bradycardie chez des chiens anesthésiés. Cette étude a évalué l'efficacité du glycopyrrolate (0.005 ou 0.01 mg/kg de poids corporel (PC) pour inhiber la bradycardie (< 65 battements/min) chez des chiens anesthésiés ($n = 40$). Suite à une administration intraveineuse (IV), la fréquence cardiaque a été déterminée après 5 min, et si les battements étaient de ≤ 70 par min la dose la plus faible était réinjectée. Une analyse de variance à deux voies prenait en considération les effets en fonction de la dose et du poids de l'animal (< 10 kg, > 10 kg), ($P < 0.05$). Le glycopyrrolate a provoqué une augmentation significative de la fréquence cardiaque et rarement une tachycardie (≤ 150 battements/min) non reliée à la dose. La grosseur du chien avait un effet significatif sur la fréquence cardiaque de base (plus élevée chez les petits), sur la fréquence suite à la première dose (plus basse chez les petits) et sur les besoins d'une réinjection (47 % chez les petits, 13 % chez les grands). Chez un autre groupe de chiens anesthésiés ($n = 20$) l'effet sur la pression artérielle du traitement de la bradycardie au glycopyrrolate a été étudié (0.01 mg/kg PC, IV), (65–85 battements/min selon les poids). Une augmentation significative de la pression systolique, diastolique et moyenne a été constatée. En conclusion, la dose efficace de glycopyrrolate est reliée à la grosseur des chiens et provoque un effet bénéfique sur la pression artérielle.

(Traduit par docteur André Blouin)

Can Vet J 1999; 40: 327–331

Introduction

Anticholinergic drugs are recommended for the treatment of vagally-induced bradycardia during anesthesia, and occasionally suggested for prevention of its occurrence, if a profound opioid analgesic is used (1–3). The antisialagogue effect of these drugs is not a significant advantage, since excessive salivation is not a common complication in modern day anesthesia. Treatment of bradycardia in the presence of opioid-supplemented anesthesia has resulted in improved cardiac output and blood pressure (BP) during controlled studies (4,5). Unnecessary use of anticholinergic drugs is discouraged because of the disadvantages of tachycardia and the associated increase in oxygen demand, which may result in arrhythmias or reduced cardiac contractility (3).

Surgical and ethical demands are resulting in increased use of more profound opioids with longer duration of effect for adequate analgesia (6). These drugs are known to enhance vagal tone and increase the frequency of bradycardia. It is likely that increased use of anticholinergic drugs will be required (7). Glycopyrrolate is gaining popularity due to its longer duration of effect and the initial impression of a lower frequency of arrhythmias (1–3).

Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1.

Address correspondence and reprint requests to Dr. Doris Dyson.

Table 1. The heart rate defined as bradycardia for Part 2 of this study

Weight range (kg)	Heart rate range (beats/min)
< 15	≤ 85
15–19	≤ 83
20–24	≤ 80
25–29	≤ 78
30–34	≤ 75
35–39	≤ 73
≥ 40	≤ 70

The purpose of this study was to assess 2 doses of glycopyrrolate in a wide weight range of bradycardic, anesthetized dogs for effectiveness and frequency of tachycardia. In another similar group of dogs, BP response to increasing heart rate (HR) was evaluated.

Materials and methods

Dogs (Part I: $n = 40$, Part II: $n = 20$) that were undergoing anesthesia for various surgical and medical procedures at the Veterinary Teaching Hospital of the Ontario Veterinary College were eligible for inclusion in the study. Patients with known cardiovascular compromise, including any significantly geriatric animal (breed dependent and at the discretion of the supervising anesthetist), were excluded.

Part I

If bradycardia (HR < 65 beats/min) occurred during anesthesia and persisted for 5 min or more, the dog was treated with glycopyrrolate (Glycopyrrolate Injection (0.2 mg/mL), Sabex, Boucherville, Quebec) randomly at either 0.005 mg/kg BW or 0.01 mg/kg BW, administered IV. The HR before treatment and 5 min following treatment was recorded as determined by electrocardiogram (ECG) (when available) or esophageal stethoscope measurement over 1 min. Any animal with a HR ≤ 70 beats/min following the initial dose of glycopyrrolate was given a second dose at 0.005 mg/kg BW, IV. The final HR was considered to be that recorded following the first dose of glycopyrrolate in responders, and 5 min following the second dose in nonresponders. Tachycardia was defined as a HR ≤ 150 beats/min. Any dog that received a significant change in stimulus during the period of assessment (surgery commencing) was eliminated from the study. Animals were divided into 2 blocks with respect to size for analysis: small (≤ 10 kg) and large (> 10 kg). A 2-way analysis of variance considered the effect of glycopyrrolate dose and animal size. A P value < 0.05 was considered significant.

Part II

Bradycardia was defined based on the weight of the dog (Table 1). If bradycardia occurred during anesthesia and persisted for 5 min or more, pretreatment BP (Dinamap oscillometric monitor, Critikon Corporation, Tampa, Florida, USA) and HR (ECG, if available, or a 1-min measurement using an esophageal stethoscope) were recorded, and the dog was treated with glycopyrrolate at 0.01 mg/kg BW, IV. The HR and BP were repeated 5 min following treatment. Any dog that received a significant change in stimulus during the assessment (surgery commencing) was eliminated from the study. A paired t-test was used to determine if a significant change in measured parameters had occurred. A P value < 0.05 was considered significant.

Table 2. Influence of dose of glycopyrrolate and patient size on baseline heart rate (HR), HR after the first dose of glycopyrrolate, the number of dogs requiring retreatment, final HR, and the number of dogs exhibiting tachycardia

	Small dogs (≤ 10 kg)		Large dogs (> 10 kg)	
Dose of glycopyrrolate (mg/kg BW, IV)	0.005	0.01	0.005	0.01
n	9	8	11	12
Baseline HR (beats/min)[a]	60 (1)	58 (2)	52 (2)	56 (2)
HR_1 (beats/min)[a]	102 (17)	76 (12)	123 (11)	109 (8)
Retreatment (n)[a]	3	7	1	2
Final HR (beats/min)	120 (9)	101 (10)	119 (7)	125 (11)
Tachycardia (n)	1	0	1	1

HR_1 = HR taken 5 min after the first dose of glycopyrrolate; Final HR = HR at 5 min after the last dose of glycopyrrolate given; Retreatment = the number of dogs requiring a second dose of glycopyrrolate because HR remained ≤ 70 beats/min after the first dose
[a]Significant difference related to size ($P < 0.05$)
Data is expressed as mean (standard error)

Table 3. Heart rate and blood pressure before (baseline) and after treatment with glycopyrrolate at 0.01 mg/kg BW, IV, in anesthetized dogs

	Baseline	Glycopyrrolate Treatment
HR	60 (2)	114 (7)[a]
Systolic BP	107 (4)	122 (4)[a]
Diastolic BP	57 (3)	73 (4)[a]
Mean BP	73 (3)	90 (3)[a]

HR = heart rate; BP = blood pressure
[a]Significantly different than baseline measurement ($P < 0.05$)
Data is expressed as the mean (standard error)
$n = 20$

Results

Part I

A significant increase in HR resulted from glycopyrrolate treatment (Table 2). The dose of glycopyrrolate produced no significant effect on HR after the first dose, the requirement for a second dose, or the final HR. The size of the dog produced a significant effect on baseline HR (higher in small dogs, $P = 0.0066$), HR following the first dose (lower in small dogs, $P = 0.0333$), and the requirement for retreatment with glycopyrrolate (higher in small dogs, $P = 0.0034$). There was no significant effect of size on the final HR. The frequency of tachycardia (HR ≥ 150 beats/min) was low in both dose groups and showed no direct relationship to dose.

Part II

In this group of dogs, systolic, diastolic, and mean BP increased significantly above baseline values following treatment with glycopyrrolate ($P \leq 0.0001$ for all) (Table 3).

Discussion

Glycopyrrolate was effective in increasing HR in most anesthetized, bradycardic dogs at the recommended dose of 0.01 mg/kg BW IV (31 out of 40 dogs from Part I and II, including 29 out of 31 large dogs) and even half of this dose resulted in an increase in HR in many dogs (16 out of 20 dogs from Part I, including 10 out of 11 large dogs). Unfortunately temperature was not gathered in this study and hypothermia may have been responsible for some of the resistance of small patients to glycopyrrolate. Small dogs tend to get more hypothermic than larger dogs during anesthesia, although attempts to maintain temperature were carried out during the study with positive warming devices (warm oat bags, hot water blankets, hot air circulators). The fact that smaller dogs were more resistant to treatment with glycopyrrolate fits the theory that smaller patients require a higher dose/kg BW for many treatments (8). This relationship is based on metabolic rate, which corresponds more to surface area than to weight. Dose may also vary with the degree of parasympathetic tone present. Anesthetic management (drugs and techniques) and physical stimuli varied within our sample. This could be responsible for the variability within and between our groups. The randomization performed, and the fact that no obvious differences between the anesthesia or the procedures between small and large dogs was apparent, reduces the chance of this explanation for the difference between dog sizes. An earlier study on dose effect of glycopyrrolate in sedated dogs that evaluated 0.01 mg/kg BW and twice this dose was able to show effectiveness with both doses, while the highest dose increased HR significantly more than the lower dose (9).

We noted several dogs that showed a 2nd degree heart block after glycopyrrolate treatment. This was a common finding with both glycopyrrolate and atropine in the study by Richards (9). A reversal of the vagal block on the sinoatrial node appeared to occur in advance of, or at a lower dose than required for, reversal of the atrioventricular node. Other explanations for this effect, and the more profound bradycardia shown with low dose atropine in humans (10), involve a peripheral anticholinesterase activity, muscarinic receptor stimulation, ganglionic influence, and acetylcholine release from nerve endings (9). This peripheral site of action appears to be best supported with evidence of HR depression in the presence of bilateral vagotomy (11). The initially accepted central vagal stimulating effect of atropine does not explain the bradycardia that has also been produced with glycopyrrolate, which is unable to cross the blood-brain barrier. The atrioventricular blocks produced in our study and that of Richards (9) were benign, and were eliminated with time or with a second dose of glycopyrrolate.

The lack of a consistent relationship between tachycardia and dose of glycopyrrolate could relate to the fact that glycopyrrolate eliminates vagal tone, and partial parasympathetic blockade may be difficult to achieve. The resulting HR following complete parasympathetic blockade should relate to the level of sympathetic drive present. Patients who are in a lighter plane of anesthesia would have an increased sympathetic drive. The procedure and anesthetic drug variability in our sample could also affect the underlying sympathetic drive. It is also a common response by anesthetists to lighten the plane of anesthesia when bradycardia is first noted. There is evidence, however, that increasing the depth of halothane anesthesia after a surgical level has been achieved produces no significant effect on HR (12). Halothane is known to dampen sympathetic drive (13), dropping the HR from awake values and reducing the ability to compensate for low BP by increases in HR. Halothane does not appear to increase parasympathetic drive as depth increases. This evidence indicates that the ideal treatment for bradycardia would not involve lightening of the plane of anesthesia, unless the patient shows other significant signs of being deep. A plausible explanation for the tachycardia following the use of glycopyrrolate in our study is an excessively light plane of anesthesia. The frequency of tachycardia that we found with glycopyrrolate (3 out of 40) was less than in Richards' study (5 out of 12), but the definition of tachycardia differed between studies and the difference in doses could have influenced the results. Richards' study also showed little difference between atropine and glycopyrrolate with respect to the HR effect or arrhythmias. Pretreatment with atropine in dogs that were anesthetized with thiamylal and halothane in 50% nitrous oxide resulted in higher HR than in our study (152 beats/min) (14). The rise in HR produced by anticholinergic treatment has been termed excess tachycardia and is greater than that produced by bilateral vagotomy (9). It has been explained by the removal of parasympathetic modulation of sympathetic outflow, a cholinergic effect at nonmuscarinic receptors that is unmasked with muscarinic receptor blockade with or without a central stimulatory effect. The cholinergic effect appears to be the one that is best supported by continued research. Although the use of atropine in humans appears to be associated with a higher frequency of tachycardia than does that of glycopyrrolate, no difference in receptor subtype sensitivity has been proven (15).

Premature ventricular contractions may occur as a result of increased oxygen demand in the face of reduced supply (16), and anticholinergic use has been shown to cause such arrhythmias (9). In theory, an increase in HR should be accompanied by an increase in oxygen consumption. Interestingly, a study done in healthy female volunteers failed to show any effect of atropine on metabolic variables, while glycopyrrolate, producing similar cardiovascular effects, resulted in a significant increase in oxygen consumption (17). Arrhythmias may be more likely to occur if anticholinergic drugs are used at the same time as other drugs, or stimuli, that cause a change in either sympathetic or parasympathetic influence (18,19). Therefore, advance treatment has been advised to reduce this possibility. It should not be assumed that premature ventricular contractions increase in severity when anticholinergic drugs are used. Epinephrine-induced arrhythmias may actually be reduced in the presence of atropine or glycopyrrolate (20). Ventricular escape beats are preferentially treated with glycopyrrolate to increase sinoatrial rate and reduce the chance for ventricular beats to occur (21).

Although bradycardia is not always associated with hypotension, the possibility exists. Clinical hypotension defined commonly as a mean BP < 60 mmHg (22) was not common in our study (only 7 out of 20 dogs showed a mean BP < 70 mmHg and showed no evidence of being in a deep anesthetic plane). A significant benefit of treatment with glycopyrrolate was an increase in BP. Blood pressure should increase by an improvement in cardiac output, since peripheral vascular effects have not been shown with anticholinergic use. Previous work showed a similar benefit in BP, secondary to cardiac output increase, when glycopyrrolate was used in the presence of opioid-induced vagal tone (4,5). None of the dogs in Part II of our study showed a fall in BP, although several showed no change in BP with treatment. It is reasonable to expect that increasing HR will have little effect on BP, if venous return is insufficient or contractility compromised. If BP is within a reasonable range, peripheral vascular resistance may fall due to baroreflexes, maintaining the BP at more normal levels. Since indirect or direct BP measurement is not commonly performed in small animal anesthetic management in a private practice setting, hypotension may go undiagnosed (23). Bradycardia is easy to diagnose, and HR is commonly monitored. Considering the lack of adverse side effects following glycopyrrolate treatment and the significant effect on BP, it is warranted to treat bradycardia, when diagnosed.

Evaluation of the anesthetic regime and circumstances surrounding the occurrence of bradycardia in our sample indicates that vagal tone was likely responsible. Bradycardia was associated with achievement of a surgical plane of anesthesia in dogs given opioid premedication, IV opioid administration, epidural opioid administration, and intermittent positive pressure ventilation. Anticholinergic use in these circumstances is appropriate. It is always important to evaluate the possibility that bradycardia is occurring as a result of some primary cause requiring immediate attention. Hypoxia, excessively deep anesthesia, significant body temperature abnormalities, electrolyte disturbances (hypokalemia), and acid-base disorders may be responsible for arrhythmias, and more direct treatment should be carried out without delay (21). Considering that glycopyrrolate increases oxygen demand, its use in the presence of hypoxia could result in significant untoward sequellae (premature ventricular contractions, cardiac arrest).

It remains to be stated that the use of glycopyrrolate to increase BP is only warranted when HR is low. There is no evidence, even in theory, that glycopyrrolate will increase BP without a significant increase in HR. Since tachycardia is rare with glycopyrrolate at the doses used here and associated with anesthesia, HR cannot be expected to increase unless it is initially low. The definition of bradycardia in dogs can differ among books, studies, and circumstances. We chose to design our own table for definition of bradycardia during anesthesia (Table 1). It is consistent with normal awake HR values in dogs that a smaller dog should have its HR maintained at a higher level than that of a larger dog. We also selected to be aggressive in the treatment of low HR and not wait until it was excessively low in our patients. This rationale likely reduced the chance of our showing significance, but with the resultant significance in BP change shown, we believe it strengthens our argument for promoting treatment. We do not recommend treatment of low HR in awake animals at the same level chosen for the anesthetized dog. A slow HR in an awake dog may be secondary to a rise in BP or a significant reduction in metabolic rate, as in the sleeping animal. During anesthesia, although metabolic rate may be reduced, most anesthetics are associated with a reduction in cardiac output and tissue perfusion, even when HR is in the normal range. To allow the HR to fall during anesthesia may decrease tissue perfusion further and risk compromising important tissues, such as the heart and kidney. We feel that our study provides evidence for taking an aggressive approach to low HR treatment. The guidelines provided in our study can be used in anesthetized dogs.

In conclusion, there is no relationship between the dose of glycopyrrolate and the final HR achieved with reversal of bradycardia or the frequency of tachycardia. Dogs ≤ 10 kg are more resistant to the effects of glycopyrrolate and are more likely to require higher than the standard dose (0.01 mg/kg BW, IV) to reverse bradycardia. It may be reasonable to treat small dogs with 0.01 mg/kg BW glycopyrrolate initially, while 0.005 mg/kg BW glycopyrrolate is usually effective in larger dogs (> 10 kg). A second dose of 0.005 mg/kg BW glycopyrrolate may be required in small or large dogs, and may be reflective of the degree of vagal tone present. A significant increase in BP is associated with effective treatment of bradycardia, and this should provide impetus for treatment. CVJ

References

1. Preanesthetics and anesthetic adjuncts. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. Lumb & Jones' Veterinary Anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1996: 183–209.
2. Drugs used in preanesthetic medication. In: Hubbell JAE, Muir WW, eds. Handbook of Veterinary Anesthesia. St. Louis: Mosby, 1989: 15–28.
3. Principles of sedation, analgesia and premedication. In: Hall LW, Clarke KW, eds. Veterinary Anesthesia. 9th ed. London: Bailliere Tindall, 1991: 51–79.
4. Ilkiw JE, Pascoe PJ, Haskins SC, Patz JD, Jaffe R. The cardiovascular sparing effects of fentanyl and atropine, administered to enflurane-anesthetized dogs. Can J Vet Res 1993; 57: 248–253.
5. Torske K, Dyson DH. The cardiovascular effects of epidural oxymorphone and oxymorphone/bupivacaine in halothane-anesthetized dogs [abstract]. Proc 6th Int Congress Vet Anesth, 1997: 108.
6. Dohoo SE, Dohoo IR. Factors influencing the postoperative use of analgesics in dogs and cats by Canadian veterinarians. Can Vet J 1996; 37: 552–556.
7. Bednarski RM. Precautions when using opioid agonists for induction of anesthesia. Vet Clin North Am Small Anim Pract 1992; 22: 273–275.
8. Kleiber M. The fire of life: An introduction to animal energetics. New York: Wiley, 1961: 179.
9. Richards DLS, Clutton RE, Boyd C. Electrocardiographic findings following intravenous glycopyrrolate to sedated dogs: a comparison with atropine. J Assoc Vet Anaesth 1989; 16: 46–50.
10. Ali-Melkkila T, Kaila T, Antila K, Halkola L, Iisalo E. Effects of glycopyrrolate and atropine on heart rate variability. Acta Anaesthesiol Scand 1991; 35: 436–441.
11. Anticholinergic drugs. In: Stoelting RK, ed. Pharmacology and Physiology in Anesthetic Practice. Philadelphia: JB Lippincott, 1987: 232–239.
12. Dyson DH. Assessment of 3 audible monitors during hypotension in anesthetized dogs. Can Vet J 1997; 38: 564–566.

13. Pavlin EG, Su JY. Cardiopulmonary pharmacology. In: Miller RD, ed. Anesthesia. 4th ed. New York: Churchill Livingstone, 1994: 125–156.
14. Muir WW. Effects of atropine on cardiac rate and rhythm in dogs. J Am Vet Med Assoc 1978; 172: 917–921.
15. Gomez A, Bellido I, Sanchez de la Cuesta F. Atropine and glycopyrrolate show similar binding patterns to M_2 (cardiac) and M_3 (submandibular gland) muscarinic receptor subtypes in the rat. Br J Anaesth 1995; 74: 549–552.
16. Katz AM. Mechanisms and abnormalities of contractility and relaxation in the failing heart. Cardiologia 1993; 38 (suppl 1): 39–43.
17. Kirvela OA, Kanto JH, Raty HM, Iisalo E. Anticholinergic drugs: effects on oxygen consumption and energy expenditure. Anesth Analg 1994; 78: 995–999.
18. Short CE. Effects of anticholinergic treatment on the cardiac and respiratory systems in dogs sedated with medetomidine. Vet Rec 1991; 129: 310–313.
19. Webb AI, Warren RG, Spencer KR. Fatal interaction between thiamylal sodium and a proprietary antidiarrheal preparation in the dog. J Am Vet Med Assoc 1983; 182: 691–693.
20. Igic R. Mechanism of epinephrine-induced dysrhythmias in rat involves local cholinergic activation. Can J Physiol Pharmacol 1996; 74: 85–88.
21. Ettinger SJ. Cardiac arrhythmias. In: Ettinger SJ, ed. Textbook of Veterinary Internal Medicine. 3rd ed. Philadelphia: WB Saunders, 1989: 1051–1096.
22. Haskins SC. Monitoring the anesthetized patient. In: Thurmon JC, Tranquilli WJ, Benson GJ, eds. Lumb & Jones' Veterinary Anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1996: 409–424.
23. Dyson DH, Maxie MG, Schnurr D. Morbidity and mortality associated with anesthetic management in small animal practice in Ontario. J Am Anim Hosp Assoc 1998; 34: 325–335.

Answers to Quiz Corner/Les réponses du Test éclair

1. e — Jugular venipuncture is almost impossible at this site because of the muscle mass covering the vein.
   e — La véniponction jugulaire est presqu'impossible à cet endroit à cause de la masse musculaire qui recouvre la veine.

2. c — The clinical signs are referrable to neuromuscular weakness and muscular pain.
   c — Les signes cliniques se rapportent à la faiblesse neuromusculaire et à la douleur musculaire.

3. d — None of the other answers is accurate.
   d — Aucune autre réponse n'est adéquate.

4. b — A mid-duodenal obstruction results in a tremendous loss of bicarbonate present in pancreatic juices and bile. This also decreases the amount of bicarbonate ion available for absorption from the intestinal tract. This loss of bicarbonate ion may result in metabolic acidosis if vomiting is severe.
   b — Une obstruction du duodénum à mi-longueur produit une perte considérable de bicarbonate présent dans le suc pancréatique et la bile. Elle diminue aussi la quantité d'ions bicarbonate disponibles pour l'absorption intestinale. Cette perte d'ions bicarbonate peut amener de l'acidose métabolique si le vomissement est sévère.

5. a

6. a

7. d — Goiter is much more likely to be seen in stillborns and young lambs than in yearlings and older sheep.
   d — Le goitre est plus susceptible de se rencontrer chez les mort-nés et les jeunes agneaux que chez les jeunes d'un an (yearlings) ou chez les animaux plus âgés.

8. e — The progesterone level in a milk sample from a cow with a mature, functional corpus luteum should be greater than 5 ng/mL. The progesterone level in the circulating plasma of the same cow should be 1 to 2 ng/mL. Because progesterone is fat soluble, it is concentrated in milk.
   e — Le taux de progestérone dans un échantillon de lait d'une vache qui a un corps jaune fonctionnel devrait être plus élevé que 5 ng/mL. Le taux de progestérone dans le plasma circulant de la même vache devrait être 1 à 2 ng/mL. Étant donné que la progestérone est liposoluble, elle est concentrée dans le lait.

9. e — Leukoderma refers to depigmentation of the skin. It is not a common crusting dermatosis.
   e — La leucodermie est une dépigmentation de la peau. Ce n'est pas une dermatose croûteuse commune.

10. d — This is the most accurate method of assessing bladder integrity.
    d — Ceci est la méthode la plus adéquate pour évaluer l'intégrité de la vessie.