Kafkas Univ Vet Fak Derg
19 (5): 779-782, 2013
DOI: 10.9775/kvfd.2013.8771

Journal Home-Page: http://vetdergi.kafkas.edu.tr
Online Submission: http://vetdergikafkas.org

RESEARCH ARTICLE

Interaction Between Phenylbutazone and Thiopental Sodium in Female Stray Dogs: The Effect on the Recovery from Anesthesia

Mahdieh RAEESZADEH [1] Hamid RAJAIAN [2]
Hamidreza FATTAHIAN [3] Shahabeddin SAFI [4]

[1] Department of Physiology and Pharmacology, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran - IRAN
[2] Department of Basic Sciences, Ward of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Shiraz University, Shiraz - IRAN
[3] Department of Surgery, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran - IRAN
[4] Department of Clinical Pathology, Faculty of Specialized Veterinary Sciences, Science and Research Branch, Islamic Azad University, Tehran - IRAN

Makale Kodu (Article Code): KVFD-2013-8771

Summary

Anesthesia often involves administration of several drugs from different classes. Drug–drug interactions may affect the duration of action of anesthetic agents. The purpose of this research was to investigate interaction between phenylbutazone and thiopental sodium in dogs. Twenty-six female stray dogs were randomly divided into two groups. Each group subdivided into two subgroups <18kg and ≥18kg. Equivalent doses of thiopental sodium were intravenously administered following the injection of 0.9% normal saline in control group and phenylbutazone via the same route in experimental group. After anesthesia, time intervals needed for the return of palpebral reflex, opening of eyes, tongue movement, stretching of limbs, head and neck movements, sitting position, trying to stand, imbalanced walking and normal walking were recorded. Results showed the average time periods in the experimental group were generally more than those in the control group. It was shown the duration of the above chronological parameters were significantly higher in heavier dogs compared to the lighter. Females generally have a larger proportion of body fat content than males. This may cause a higher volume of distribution and a longer elimination half-life for thiopental in female dogs. This interaction with phenylbutazone may be due to an increase in the unbound form of thiopental sodium and its quicker distribution into the brain and a longer duration of anesthesia.

Keywords: *Drug interaction, Thiopental sodium, Phenylbutazone, Anesthesia, Dog*

Kısırlaştırılmış Dişi Köpeklerde Fenilbutazon ve Thiopental Sodyum Etkileşimi: Anesteziden Çıkışa Etkisi

Özet

Aneztezi çoğu zaman birden fazla değişik sınıftan ilaçların uygulanmasını içerir. İlaçlar arası etkileşim anestezik maddenin etki süresini etkileyebilir. Bu çalışmanın amacı köpeklerde fenilbutazon ve thiopental sodyumun etkileşimini araştırmaktır. Yirmi altı kısırlaştırılmış dişi kopek rastgele iki gruba ayrıldı. Her bir grup <18kg ve ≥18kg olmak üzere iki altgruba ayrıldı. Eşit dozlarda olmak üzere thiopental sodyum control grubundakilere intravenöz %0.9 tuzlu su verilmesinin ardından, çalışma grubundakilere ise aynı yolla fenilbutazon verilmesini takiben intravenöz olarak uygulandı. Anesteziyi takiben göz kapağı refleksi, gözünü açma, dilini hareket ettirme, ayaklarını uzatma, kafa ve boyunu hareket ettirme oturma pozisyonunu sağlama, kalkmaya çalışma, dengesiz yürüme ve norma yürüme için geçen süreler kaydedildi. Sonuçlar çalışma grubundaki hayvanlarda kaydedilen ortalama sürelerin genel olarak control grubundaki hayvanlardan daha uzun olduğu gösterdi. Yukarıda belirtilen parametrelerde sürelerin daha ağır köpeklerde hafif olanlara oranla önemli derecede daha uzun olduğu gözlemlendi. Dişiler genellikle erkeklere oranla daha fazla vücut yağına sahiptir. Bu durum, dişilerde daha fazla miktarda yayılmaya ve thiopentalin yarılanma ömrü için daha uzun zamana ihtiyaç doğurabilir. Fenilbutazon ile etkileşim, thiopental sodyumun bağsız formundaki artışa ve onun daha hızlı olarak beyine yayılmasına ve daha uzun anestezi süresine bağlı olabilir.

Anahtar sözcükler: *İlaç etkileşimi, Thiopental sodyum, Fenilbutazon, Anestezi, Köpek*

İletişim (Correspondence)
+90 464 6127317
vet_mr@yahoo.com

INTRODUCTION

Anesthesiaisan important subject in veterinary medicine and is used for a wide range of circumstances in animals due to animals' unwillingness to cooperate with certain diagnostic or therapeutic procedures [1]. Amonganimals, cats and dogs are frequently anesthetized for surgical procedures [1]. Anesthesia often involves administration of several agents belonging to different classes of drugs [1]. In addition, many patients should take a number of drugs related to their surgical condition or for other medical situations [1-3]. Unexpected events may occur when the drugs are administered simultaneously. Thus, there is a considerable potential for drug interactions to occur, some of which may be potentially harmful to the patients. This may be accompanied by cardiovascular and respiratory depression and a delay in recovery for hours or even days [2,3].

Sleep may be prolonged in patients with increased central nervous system responses to depressant drugs, e.g., patients who are hypothermic; or factors affecting redistribution and metabolism of drugs, e.g., patients who have hepatic or renal dysfunction [1]. Patient's gender, age, weight and drug interaction may be important factors influencing recovery from general anesthesia [2-4]. Nowadays, medications having minimal side effects and with short recovery period are mostly used to induce anesthesia [5].

Animal studies and controlled studies in human volunteers suggest that there are differences in the speed of recovery from various anesthetics [6]. Thiopental sodium is an intravenous short-acting thiobarbiturate with rapid onset of action [7].

Phenylbutazone is indicated for the relief of musculo-skeletal inflammation and mild to moderate somatic or visceral pain particularly in post-operative pain in dogs, horses, and cattle [8]. In certain situations, thiopental may be used concurrently with phenylbutazone. Therefore, the aim of the present study was to examine the possible interactions between phenylbutazone and thiopental in dogs as it may change various post-anesthetic signs.

MATERIAL and METHODS

Thiopental sodium (0.5 g vials; Sanduz, Austria, Lot No. 150566), phenylbutazone (Vetanyl 20%, RayhanDaroo, Tehran, Iran), normal saline (sodium chloride 0.9%, Martyr Judge Serum Company, Tabriz, Iran) were purchased from local suppliers. Twenty-six female stray dogs of one to two year old weighing 8 to 23 kg were used. Twenty six dogs were divided into two groups (control and experimental) and divided into two subgroups (6 dogs < 18 kg and 7 dogs ≥ 18 kg). After a physical check-up of all animals,blood samples were taken and were tested for CBC, Hb and PCV and for several biochemical parameters (total protein, ALT and AST) in order to ensure about their health. The first group received 0.1 ml/kg normal saline five minutes before administration of thiopental sodium (5%) with a dosage of 17 mg/kg. Dogs in the second group were injected phenylbutazone (20%, 0.1 ml/kg) five minutes prior to anesthesia (induced by the same dosage of sodium thiopental). After injection of sodium thiopental, the times required for the return of various parameters such as palpebral reflex (PR), tongue movement (TM), stretching of limbs (SL), opening of eyes (OE), head and neck movement (HNM), sitting position (SP), trying to stand (TTS), imbalanced walking (IW), and normal walking (NW) were recorded.

Analysis of Data

All results are expressed as mean ± SEM and were analyzed using one-way ANOVA followed by Tukey's test. P value of < 0.05 was considered statistically significant.

The study was approved by the AnimalEthics Committee of the Iranian laboratory animal ethic frameworks under the referencecode IAEC 1-12/2.

RESULTS

Biochemical and hematological parameters were depicted in *Table 1*. Mostly, the measured values are within the normal ranges reported so far [9-11]. The durations for various chronological parameters following anesthesia induced by thiopental in female subjects in both control and experimental groups are illustrated in *Table 2*. The average times for the return of PR and OE in the control group were around 4 and 12 min, respectively. The corresponding valuesin the experimental group were approximately 15 and 25 min *(Table 2)*. The average times required for the TM and SL in the control group were around 12 and 12 min, but were recorded to be approximately 24 and 24 min in the experimental group *(Table 2)*. The average times for HNM and SP were found to be approximately 15 and 21 min in the control group, while corresponding values of 31 and 41 min were recorded in the experimental group *(Table 2)*. Times required for TTS and IW in the control

Table 1. *Hematology and blood biochemical parameters of female dogs*
Tablo 1. *Dişi köpeklerin hematoloji ve kan biyokimyası parametreleri*

Parameters	Observed Values	
	Mean±s.e.m. (n=26)	Range
Body weights (kg)	16.7±0.7	12-30
WBC (x 10^3 cells/µL)	12.5±0.8	4.8-15.4
RBC (x 10^6 cells/µL)	6.9±0.5	4.2-12.3
Hb (g/dL)	11.0±0.4	8.6-14.3
PCV (%)	35.2±2.5	21-60
Total Protein (g/dL)	5.7±0.2	4.3-6.9
ALT (IU/L)	23.5±1.4	12.9-39.1
AST (IU/L)	20.3±1.3	10.8-30.5

group were around 24 and 32 min, but were found to be around 43 and 50 min in the other group *(Table 2)*. Finally, the average time required for NW was about 52 and 67 min in the control and experimental groups, respectively *(Table 2)*. Various parameters related to the return of the anesthesia in female dogs in control and experimental groups with respect to their body weights are shown in *Table 3*. Average times for various parameters including PR, OE, SL, TM, HNM, SP, TTS, IW and NW were around 4, 11, 10, 10, 13, 18, 20, 27 and 58 min in the control group weighting less than 18 kg body weight, but the corresponding values in the experimental group were obtained to be 11, 23, 23, 21, 28, 42, 43, 49 and 67 min *(Table 3)*. The above values for dogs weighing ≥18 kg were respectively found to be 4, 11, 13, 13, 16, 24, 26, 36 and 47 min in the control group. However, the corresponding values in the experimental group were recorded to be 19, 26, 25, 27, 34, 40, 43, 51 and 66 min, respectively *(Table 3)*.

Table 2. *Comparison of times (minutes) required for the return of various parameters following anesthesia induced by sodium thiopental in female dogs*

Tablo 2. *Sodyum thiopental ile anestezi edilen dişi köpeklerde kaydedilen (dakika olarak) çeşitli parametrelerin karşılaştırılması*

Parameters	Groups (body weight)	
	I[1] (17.3±1.2 kg)	II[2] (16.2±0.7 kg)
Palpebral reflex	4.2±0.6	15.2±3.8*
Opening of eyes	11.5±2.0	25.0±3.9*
Tongue movement	12.2±1.8	24.5±3.5*
Stretching of limbs	12.5±1.7	24.3±3.4*
Head and neck movement	14.9±1.7	31.2±4.6*
Sitting position	21.7±2.1	41.4±5.0*
Trying to stand	23.9±2.7	43.0±5.5*
Imbalanced walking	32.8±5.4	50.3±5.6*
Normal walking	52.3±6.0	67.1±6.4

*[1] Normal saline (0.1 ml kg^{-1}) 5 min before the injection of sodium thiopental (17 mg kg^{-1}), [2] Phenylbutazone (20 mg kg^{-1}) 5 min before the injection of sodium thiopental (17 mg kg^{-1}), [3] Mean ± s.e.m. (n=13), * Statistically different (P<0.05) from the corresponding value in the control group*

DISCUSSION

Anesthesia is used for a wider range of circumstances in animals than in people, due to animals' unwillingness to cooperate with certain diagnostic or therapeutic procedures. Selection of an anesthetic protocol with minimum complications is quite necessary and should be based on scientific evidences. For example, drug–drug interaction can lead to an increase or a decrease in the anesthetic requirement or may prolong duration of action of anesthetic agents [12,13]. Non-steroidal anti-inflammatory drugs (NSAIDs) have the potential for both pharmacokinetic and pharmacodynamic interactions with several anesthetic agents through interfering with their plasma protein binding and/or their analgesic effects [14]. The interaction between thiopental sodium (a drug that is used for the induction of general anesthesia) and phenylbutazone (among NSAIDs) was studied in the present study.

Ghoneim et al.[8] showed in a study that uremic and sulfonamide-pretreated rats had significantly higher levels of ^{14}C in their brain and heart and more free thiopental was present in their plasma at each time than did control animals. They concluded that reduced protein binding of thiopental sodium leads to accelerated distribution and increased drug concentrations in the brain and heart. According to our study, dogs in the control group had faster

Table 3. *Comparison of times (minutes) required for the return of various parameters following anesthesia induced by sodium thiopental in female dogs weighing <18 kg or ≥18 kg*

Tablo 3. *Sodyum thiopental ile anestezi edilen <18 kg veya ≥18 kg dişi köpeklerde kaydedilen (dakika olarak) çeşitli parametrelerin karşılaştırılması*

Parameters	Groups			
	I[1]		II[2]	
	Body Weights (kg)		Body Weights (kg)	
	<18 14.3±0.6[3] (n=6)	≥18 19.2±1.7 (n=7)	<18 14.2±0.5 (n=6)	≥18 18.4±0.8 +(n=7)
Palpebral reflex	4.6±0.8	3.9±0.9	11.4±3.1*	19.5±7.3**
Opening of eyes	11.0±0.6	11.8±3.2	23.7±5.2*	26.5±6.3**
Tongue movement	10.0±1.2	13.6±2.8	21.7±4.6*	27.8±5.3*
Stretching of limbs	10.6±0.9	13.8±2.7	23.6±5.1*	25.2±4.9*
Head and neck movement	13.0±1.2	16.1±2.7	28.6±6.9*	34.2±6.3*
Sitting position	18.2±1.2	23.9±3.1	42.4±8.2*	40.2±6.0*
Trying to stand	20.6±3.4	26.3±3.6	42.9±8.4*	43.2±7.6*
Imbalanced walking	27.8±3.8	36.4±8.2	49.0±8.8*	51.8±7.4*
Normal walking	58.0±7.8	47.5±8.5	67.6±11.0	66.5±6.7*

[1] Normal saline 5 min before the injection of sodium thiopental (n=13), [2] Phenylbutazone 5 min before the injection of sodium thiopental (n=13), [3] Mean ± s.e.m. (n=13), Statistically different (P<0.05; ** P<0.01) from the corresponding values in the control group*

recovery times than dogs in the experimental group and the differences in the chronological parameters measured were mostly significant (P<0.05). This may lead to drug interaction between thiopental and phenylbutazone and cause to increase free-form of thiopental.The increased concentration of thiopental can be attributed to the interaction between phenylbutazon and thiopental.

Yu et al.[15] claim that sulfadimethoxine causes displacement of thiopental from plasma proteins which significantly increases the free fraction of thiopental. This result may explain the significant increase in V_{ss} and the decrease of both beta and intrinsic clearances. Phenylbutazone given during the pre-surgical period has been reported to increase the intensity and duration of thiamylal anesthesia in horses [16]. A possible mechanism of competitive plasma protein binding has been suggested in this respect.

In obese patients, thiopental has an increased V_d and a longer elimination half-life ($t_{1/2}$), but Cl values are unchanged. It was stated in as long ago as 1969 that thiopental dosage should be based on lean body mass (LBM) [17]. For lipid-soluble drugs, such as opioids and benzodiazepines, the volume of distribution is generally larger in women, but for water-soluble drugs, such as muscle relaxants, it is smaller [18].

On the basis of the above evidences and findings of the present study (the average times required for various chronological parameters were mostly less when thiopental was injected alone compared to those anesthetized following phenylbutazone administration, and the fact that this variation is more pronounced in the heavier dogs) may support this hypothesis that the interaction between these two drugs is most probably due to competition for protein binding sites. A higher concentration of the unbound form of thiopental will increase distribution of the drug to the tissues, particularly to the fat deposits and brain due to the lipid soluble nature of barbiturates. Redistribution of thiopental will extend the duration of action of the drug and, therefore, the duration for recovery period will increase in dogs receiving phenylbutazone before induction of anesthesia by sodium thiopental. This is in contrast to the usual expectation of similar interactions between less lipid soluble drugs which leads to increased unbound form of drug. The consequence of itis greater pharmacological activity andless duration of action.

In conclusion, interaction between phenylbutazone and thiopental sodium can increase the unbound form of thiopental which has pharmacokinetics impact on the duration of action of the anesthetic drug. Considering the drug interaction can increase free form and Vdof thiopentalwhich is a slower redistribution phase when the drug is taken up by body fat and partitioned out of the CNS. Multitude of factors that may influence recovery, body weight effect appears to be strong one. Female dogs have generally a larger proportion of body fat, redistribution of the drug from adipose tissue to brain will take longer and recovery time will be higher in the heavier female dogs.

Acknowledgement

Funding for this work was partially provided by Shiraz University which is greatly appreciated. We are grateful to J. Jalaei, M. Goharinia, H. Safari, I. Haghani, N. Safi and N. Ameri for their technical assistance.

REFERENCES

1. Bednarski R, Grimm K, Harvey R, Victoria M, Lukasik W, Penn S, Sargent B: AAHA Anesthesia Guidelines for Dogs and Cats. *J Am AnimHospAssoc,* 47, 377-385, 2011.

2. Myles PS, McLeod A, Hunt J, Fletcher H: A cohort study of gender differences in speed of emergence and quality of recovery after anesthesia. *B M J,* 322, 710-711, 2001.

3. Moller DH, Glass PSA: Should a patient's gender alter the anesthetic plan? *Curr. OpinAnesthesiol,* 16, 379-383, 2003.

4. Pleym H, Spigset O, Kharasch ED, Dale O: Gender differences in drug effects: Implications for anesthesiologists. *Acta Anaesthiol Scand*, 47, 241-259, 2003.

5. Branson KR: Injectable anesthetics. **In,** Adams R (Ed): Veterinary Pharmacology and Therapeutics. 8th ed., p.213-268, Ames, Iowa State University Press, 2001.

6. Lockhart SH, Cohen Y, Yasuda N, Freire B, Taheri S, Litt L, Eger EI II: Cerebral uptake and elimination of desflurane, isoflurane and halothane from rabbit brain: An *in vivo* NMR study. *Anesthesiol,* 74, 575-580, 1991.

7. Kataria S, Mehra L, Badiye A: A Study of pharmacokinetics of sodium thiopental in rats by histological examination of kidney and heart. *Res J Pharmaceut Sci,* 1 (2): 1-6, 2012.

8. Ghoneim MM, Pandya HB, Kelley SE, Fischer LJ, **Corry RJ:** Binding of thiopental to plasma proteins: Effects on distribution in the brain and heart. *Anesthesiol,* 45 (6): 635-639, 1976.

9. Ariyibi AA, Oyeymi MO, Ajadi RA: A comparative study of some hematology and biochemical parameters of clinically healthy Alsatian and local dogs. *Afr J Biomed Res,* 5, 145-147, 2011.

10. Choi SY, Hwang JS, Kim IH, Hwang DY, Kang HG: Basic data on the hematology, serum biochemistry, urology, and organ weights of beagle dogs. *Lab Anim Res,* 27 (4): 283-291, 2011.

11. Khan SA, Epstein JH, Olival KJ, Hassan MM, Hossein MB, Rahman KBMA, Elahi MF, Mamun MA, Haidar N, Yasin G, Desmond J: Hematology and serum chemistry reference values of stray dogs in Bangladesh. *Open Vet J,* 1, 13-20, 2011.

12. Klide AM, Rivas C, Peters J: Effect of atropine sulfate on thiopental-induced sleeping time in the dog. *JAVMA,* 164, 1029, 1974.

13. Grimm KA, Thurmon JC, Olson WA, Tranquilli WJ, Benson GJ: The harmacodynamics of thiopental, medetomidine, butorphanol and atropine in beagle dogs. *J Vet PharmacolTher,* 21, 133-137, 1998.

14. Hu OY, Chu KM, Liu HS, Chiao SF, Ho W, Ho ST: Reinduction of the hypnotic effects of thiopental with NSAIDs by decreasing thiopental plasma protein binding in humans. *ActaAnaesthesiolScand,* 37, 258-261, 1993.

15. Yu HY, Sawada Y, Sugiyama Y, Iga T, Hanano M: Effect of sulfadimethoxine on thiopental distribution and elimination in rats. *J Pharm Sci,* 70 (3): 323-326, 1981.

16. Young DB, Ewing PJ, Burrows GE, Lessley BA, Clarke CR, Shawley RV: Effects of phenylbutazone on thiamylal disposition and anesthesia in ponies. *J Vet Pharmacol Therap,* 17, 389-393, 1994.

17. Bruce A, Andersson M, Arvidsson B, Isaksson B: Body composition. prediction of normal body potassium, body water and body fat in adults on the basis of body height, body weight and age. *Scand J Clin Lab Inves*t, 40, 461-473, 1980.

18. Homer TD, Stanski DR: The effect of increasing age on thiopental disposition and anesthetic requirement. *Anesthesiol*, 62, 714-724, 1985.