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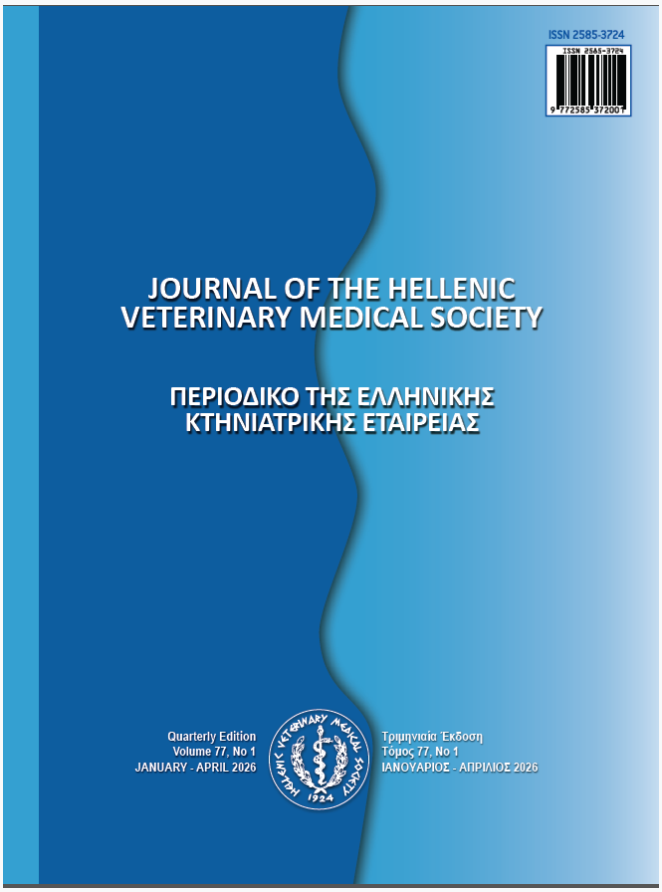

A retrospective study of propofol requirements for induction of anaesthesia in paediatric and geriatric dogs and cats.

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Retrospective study
Αναδρομική μελέτη

A retrospective study of propofol requirements for induction of anaesthesia in paediatric and geriatric dogs and cats

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ABSTRACT: The aim of this study was to investigate if propofol requirements for induction of anaesthesia are lower in paediatric and geriatric dogs and cats than in adults. Based on 5-year retrospective data, 3,266 dogs' and 606 cats' anaesthetic records were included in the study. Animals induced with propofol were grouped according to premedication and age. A Kolmogorov-Smirnov test revealed non-parametric data, while a Kruskal-Wallis and a Mann-Whitney test were used for comparisons. Paediatric and geriatric animals required significantly different propofol doses compared to adults. Premedication type and indication for anaesthesia also influenced propofol dose requirements. According to our study neonatal and paediatric dogs and cats require a higher dose of propofol for induction of anaesthesia when compared to adults and geriatrics, while geriatric patients require a lower dose compared to other groups. This finding comes in contrast to suggestions in veterinary literature that paediatric patients require a lower dose of propofol compared to adult animals. When propofol is used as a sole agent for induction of anaesthesia, patient age can affect the total amount of drug used.

Keyword: paediatric; geriatric; propofol; dog; cat; induction; anaesthesia

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INTRODUCTION

The administration of general anaesthesia in paediatric and geriatric patients is a concern for veterinarians today as they represent high risk patient groups (Redondo et al., 2024). It has been suggested in the veterinary literature that the propofol dose required for general anaesthesia induction in paediatric and geriatric dogs and cats is lower than that required in adult patients (Grubb, Tamara L.; Perez Jimenez, Teresa E.; Pettifer, Grant R., 2015a). This study was prompted by the author's clinical observations that paediatric patients require higher doses of propofol than adults.

Propofol is a widely used non-barbiturate general anaesthetic drug utilized in both human and veterinary medicine (Henao-Guerrero and Riccó, 2014). The anaesthetic properties of propofol are due to its agonistic action on the gamma-aminobutyric acid (GABA) receptor complex by binding to the β-subunit of the $GABA_A$ receptor (Sahinovic et al., 2018). Due to its pharmacokinetic properties, particularly the lack of cumulative effects, propofol is often used in dogs and cats for chemical restraint to perform short-duration diagnostic procedures, for anaesthesia induction with tracheal intubation, and for maintaining anaesthesia with continuous intravenous infusion or small repeated doses ((Chatdarong et al., 2006; Sahinovic et al., 2018)).

Propofol exhibits a rapid onset of action (about 30 seconds) and short duration of action (2-8 minutes) (Butterworth, John F.; Mackey, David C.; Wasnick, John D., 2013). The rapid uptake by tissues and extrahepatic metabolism contribute to quick recovery even after prolonged use, so the elimination of the drug is not significantly affected in patients with cirrhosis or renal failure (Adembri et al., 2007).

Newborns and paediatric patients have incomplete organ development, reduced response capability of various organ systems, and lower required doses of certain anaesthetic drugs. The physiological differences between newborns and adult animals result in differences in drug pharmacokinetics and pharmacodynamics (Grubb, Tamara L.; Perez Jimenez, Teresa E.; Pettifer, Grant R., 2015a). Plasma albumin levels in newborns are low, affecting drug binding and overall pharmacodynamics (Pascoe and Moon, 2001). Propofol binding to plasma proteins is very high (96-98%) in all species, primarily to albumin (95%), but only very low albumin concentrations can alter propofol binding (Bester, Lynett, 2009).

Blood-brain barrier permeability is five to six times higher in newborns than in adults (Pascoe and Moon, 2001), allowing greater drug quantity to reach the brain (Grubb, Tamara L.; Perez Jimenez, Teresa E.; Pettifer, Grant R., 2015a).

At birth, the amount of intracellular and extracellular water relative to total body mass is at its highest (70-75%), and fat content is lower than in adults. Consequently, newborns and infants have a larger volume of distribution (Amaniti, 2012). In healthy children, the volume of distribution is approximately 50% higher compared to adults (343 ml/kg vs. 228 ml/kg), and clearance is double that of adults (57 ml/kg/min vs. 27 ml/kg/min) (Marsh et al., 1991). These findings imply that paediatric patients require higher single and maintenance doses to achieve stable drug levels in the blood (Amaniti, 2012). Lipid-soluble drugs would be expected to have a smaller volume of distribution, but certain lipid-soluble drugs, like propofol, show an increased volume of distribution in very young animals. This is thought to be due to increased cardiac output at this age, along with propofol distribution to highly perfused tissues, increasing the volume of distribution (Pascoe and Moon, 2001).

In paediatric patients older than two years in humans until adulthood, blood flow to the liver and kidneys is high, resulting in shorter half-lives of most anaesthetic drugs compared to adults. This, combined with the increased volume of distribution, results in higher propofol doses required in human paediatric patients (Amaniti, 2012).

Age significantly affects the dose required for general anaesthesia induction, which is maximal in humans under two years of age and decreases with age. Additionally, the dose of propofol required for loss of consciousness decreases with age in unpremedicated children (Aun et al., 1992).

One reason for the reduced rate of drug metabolism and excretion in geriatric patients is decreased cardiac output, leading to reduced hepatic blood flow, and thus less drug reaching the liver for metabolism and excretion. This can result in prolonged drug action and consequently extended patient recovery (Grubb, Tamara L.; Perez Jimenez, Teresa E.; Pettifer, Grant R., 2015b). Furthermore, in geriatric patients, liver mass decreases by up to 50%, resulting in reduced availability of hepatic enzymes, coagulation factors, plasma proteins, and glucose (Baetge and Matthews, 2012). Reduced hepatic

clearance, along with decreased glomerular filtration and excretory capacity of the kidneys, observed in geriatric patients, leads to an increased half-life and duration of drug action. As a result, the metabolism of lipid-soluble drugs, particularly anaesthetics, is significantly reduced (Hughes, 2008).

Additionally, geriatric patients have decreased clearance rates and smaller central compartment volume (Kirkpatrick et al., 1988; Shafer et al., 1988). They exhibit reduced water and muscle mass and increased fat content, leading to changes in the distribution of water- and lipid-soluble drugs (Baetge and Matthews, 2012). Overall water loss results from reduced intracellular water and plasma volume. Intravenous administration of anaesthetic drugs in a reduced volume of distribution results in initially increased plasma concentrations, justifying the lower drug doses required in geriatric patients (Grubb, Tamara L.; Perez Jimenez, Teresa E.; Pettifer, Grant R., 2015b).

The propofol dose required for anaesthesia induction in geriatric dogs has been proven to be lower than the manufacturer's recommended dose, with slower removal (Reid, 1996).

The purpose of this study was to retrospectively investigate whether the propofol requirements for anaesthesia induction (to achieve tracheal intubation) are lower in paediatric and geriatric dogs and cats compared to adult animals. A secondary aim was to investigate how the indication for anaesthesia, sex or premedication protocol affects the propofol requirements in these patients when compared to adults. The null hypothesis was that paediatric dogs and cats have lower propofol requirements for anaesthesia induction compared to adult dogs and cats, and that geriatric dogs and cats have lower propofol requirements for anaesthesia induction compared to adult dogs and cats.

MATERIALS AND METHODS

This is a retrospective study of canine and feline patients presented to the Anesthesiology and Intensive Care Unit of the Companion Animal Clinic of the Department of Veterinary Medicine, School of Health Sciences, Aristotle University of Thessaloniki (A.U.TH.) for general anaesthesia. The study included 3,266 dogs and 607 cats presented to the Companion Animal Clinic for general anaesthesia for various reasons from January 1, 2019, to January 1, 2024. Data for these five years were collected retrospectively from the medical records maintained at the clinic.

Inclusion criteria: only cases where propofol was administered intravenously (IV) as the sole agent for general anaesthesia induction were included. Data collected from each anaesthesia record included the patient's registry number, breed, sex, body weight, age, indication for general anaesthesia, type and dose of sedative and analgesic drugs administered before propofol anaesthesia induction, the propofol dose required for tracheal intubation, and any complications encountered. These data were recorded in spreadsheets (Microsoft Excel spreadsheets).

Exclusion criteria: cases for which data was missing in the anaesthetic record were excluded from the study. Cases of animals with body condition scores ≥6 or ≤3 were excluded from the study. Also, cases that received a co-induction with another agent and propofol were excluded as well as cases where propofol was not used as an induction agent.

Regarding patient groups:

- animals were allocated to four groups according to age. The first age group consisted of neonates from the first to the eleventh week of life, the second group consisted of young animals from the eleventh week to six months of life, the third group consisted of adult animals from six months of life until considered elderly, and the fourth group consisted of elderly animals that had reached 75% of their life expectancy (Rigotti and Brearley, 2016). Cats, due to their similar size, are considered elderly from ten years of age and older (Guedes et al., 2018).

A further categorization was performed to allow comparison of the allocated animals in each different category.

- animals were allocated to six categories according to the indications for anaesthesia: orthopedic surgeries, soft tissue surgeries, spinal surgeries, ophthalmic surgeries, dental surgeries, and radiographic/diagnostic examinations.
- animals were allocated to three categories according to premedication drugs: animals that did not receive any premedication except propofol for anaesthesia induction, animals that received an α_2-agonist alone or in combination with other drugs, and animals that received any other drugs except an α_2-agonist. The type and dose of premedication drugs administered before propofol anaesthesia induction were recorded.

In dogs, life expectancy varies by size. Small-

sized dogs have a longer life expectancy, while larger dogs have a shorter life expectancy. Therefore, dogs were classified as elderly based on body size: small dogs from eleven years of age and older, medium-sized dogs from ten years and older, large dogs from eight years and older, and giant dogs from seven years and older (Siegal and Barlough, 1995).

Finally, small dogs were considered those that weighed less than nine kg, medium-sized dogs that weighed nine-nineteen kg, large-sized dogs those that weighed twenty-forty kg, and giant-sized dogs that weighed over forty kg (Urfer et al., 2020). These categories included animals with body condition scores of 4 and 5, which were neither obese (score ≥6) nor emaciated (score ≤3) (Laflamme, Dottie., 1997). If an animal's anaesthesia record indicated obesity or emaciation, the animal was excluded from the study.

The collected digital data were statistically processed. The Kolmogorov-Smirnov test was used to check for normality of data distribution. Since the variables did not follow a normal distribution, non-parametric tests were used, and the results are presented as median, maximum, and minimum values. Differences between variables were tested using the Kruskal-Wallis test, and pairwise comparisons were made using the Mann-Whitney test. A significance level of α=0.05 was set for all tests, except for pairwise comparisons corrected with Bonferroni adjustment, where α=0.0083 was set for the variables age, premedication, and propofol dose in mg/kg b.w., and α=0.003 for the variables sex and anaesthesia indication. All statistical calculations were performed using specialized software (IBM SPSS Statistics 24).

RESULTS

This retrospective study included 3,266 dogs and 606 cats that underwent general anaesthesia. The number of patients were recorded separately for dogs and cats. Regarding breed for dogs the highest prevalence was mix breed (1471/3266) with no other breed exceeding more than 150/3266 animals (table A.1), while for cats 552/606 were domestic shorthair table A.2. Regarding sex 51% of dogs were male (1698/3266) and 49% female (1568/3266) (table A.3)] while cats were 50% male (302/606) and 50% female (304/606) (table A.4)]. Indications for anaesthesia (tables 1 and 2) were recorded separately for dogs and cats. Animals were divided into four age groups in three different pre-medication categories (tables 3 and 4). Drugs used for premedication included medetomidine, dexmedetomidine, xylazine, midazolam, acepromazine, butorphanol, morphine, pethidine, methadone, buprenorphine, and tramadol.

Table 1. The number of dogs included in the study that were divided by indications for anaesthesia.

Indication	n
Radiographic/diagnostic examinations	1049
Soft Tissue surgery	1318
Spinal surgery	130
Dentistry	378
Orthopedic surgery	328
Ophthalmic Surgery	63
Total	3266

Table 2. The number of cats included in the study that were divided by indications for anaesthesia.

Indication	n
Radiographic examinations	164
Soft Tissue surgery	284
Spinal surgery	5
Dentistry	84
Orthopedic surgery	53
Ophthalmic Surgery	16
Total	606

Regarding patient sex, no statistically significant difference in propofol dose required for anaesthesia induction was found between sexs when compared according to the premedication category, as shown in tables 5 and 6.

In relation to indication for anaesthesia, no statistically significant difference was found in propofol dose required for anaesthesia induction in dogs and cats in the no premedication group (tables 7 and 8) or in cats in the α_2-agonist group (table 10). However, a statistically significant difference was found in the α_2-agonist group in dogs (table 9) between radiographic/diagnostic examinations with a median propofol dose of 2.19 mg/kg b.w. and dental surgeries with a median propofol dose of 2 mg/kg b.w. ($p<0.0005$) and between dental surgeries and spinal surgeries with a median propofol dose of 2.41 mg/kg b.w. ($p<0.0005$).

In the other drugs group in dogs (table 11), a

Table 3. The number of dogs in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) and which were allocated to three different premedication categories when divided by age.

Age	Premedication			
	No premedication	α_2-Agonist	Other drugs	Total
Neonatal	5	9	27	41
Paediatric	6	189	50	245
Adult	54	1938	353	2345
geriatric	34	333	268	635
Total	99	2469	698	3266

Table 4. The number of cats in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) and which were allocated to three different premedication categories when divided by age.

Age	Premedication			
	No premedication	α_2-Agonist	Other drugs	Total
Neonatal	2	5	8	15
Paediatric	4	50	14	68
Adult	18	365	69	452
geriatric	3	44	24	71
Total	27	464	115	606

Table 5. Descriptive statistics of dogs in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) and which were allocated to three different premedication categories when divided by sex.

Premedication	Number of dogs M/F (total)	Propofol (mg/kg b.w.)			Mann-Whitney Test	
		Median M/F	Min M/F	Max M/F	U	Significance (Monte Carlo)
No Premedication	50/49 (99)	2.50/3.89	0.99/0.97	14.44/13.64	976.500	0.08
α_2-Agonists	1334/1135 (2469)	2.08/2.11	0.20/0.43	17.50/18.60	736758.00	0.25
Other Drugs	314/384 (698)	2.72/2.85	0.24/0.38	16.67/15.22	58011.00	0.37

Table 6. Descriptive statistics of cats in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) and which were allocated to three different premedication categories when divided by sex.

Premedication	Number of cats M/F (total)	Propofol (mg/kg b.w.)			Mann-Whitney Test	
		Median M/F	Min M/F	Max M/F	U	Median M/F
No Premedication	16/11 (27)	4.91/4.00	2.00/1.00	30.00/6.90	64.00	0.24
α_2-Agonists	216/248 (464)	2.24/2.39	0.32/0.60	14.00/15.63	24788.50	0.16
Other Drugs	370/45 (115)	2.91/4.00	1.03/1.00	25.00/34.00	1232.50	0.052

Table 7. Descriptive statistics of dogs that did not receive any premedication in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) divided by indication for anaesthesia.

NO PREMEDICATION						
Indication for anaesthesia	N	Propofol (mg/kg b.w.)			Kruskal-Wallis Test	
		Median |	Min	Max	X^2	Significance (Monte Carlo)
Radiographic Examinations	72	3.82	0.99	14.44	5.466	0.235
Soft Tissue Surgery	20	2.06	0.97	10.00		
Dentistry	3	3.63	1.48	5.56		
Orthopedic Surgery	3	2.00	2.00	3.24		
Ophthalmic Surgery	1					
Total	99					

Table 8. Descriptive statistics of cats that did not receive any premedication in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) divided by indication for anaesthesia.

NO PREMEDICATION				
Indication for anaesthesia	N	Propofol (mg/kg b.w.)		
		Median |	Min	Max
Soft Tissue Surgery	27	4.37	1.00	30.00

Table 9. Descriptive statistics of dogs that received an a_2-agonist based premedication protocol in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) divided by indication for anaesthesia.

α_2-Agonists						
Indication for anaesthesia	N	Propofol (mg/kg b.w.)			Kruskal-Wallis Test	
		Median	Min	Max	X^2	Significance (Monte Carlo)
Radiographic Examinations	832	2.19	0.24	18.60	21.579	0.001
Soft Tissue Surgery	955	2.05	0.20	17.50		
Spinal Surgery	103	2.41	0.88	7.67		
Dentistry	293	2.00	0.43	9.38		
Orthopedic Surgery	243	2.10	0.50	6.82		
Ophthalmic Surgery	43	2.12	0.80	4.26		
Total	2469					

statistically significant difference in propofol dose required for radiographic examinations with a median propofol dose of 2.67 mg/kg b.w. and spinal surgeries with a median propofol dose of 4 mg/kg b.w. ($p<0.001$) was found, soft tissue surgeries with a median propofol dose of 2.72 mg/kg b.w. and spinal surgeries, and between orthopaedic surgeries with a median propofol dose of 2.92 mg/kg b.w. and spinal surgeries ($p<0.0005$), while in cats (table 12) between radiographic examinations with a median of 5 mg/kg b.w. and soft tissue surgeries with a median of 2.94 mg/kg b.w. ($p<0.001$).

Regarding the amount of propofol required among the age groups and according to premedication, as shown in table 13, in the population of dogs that did not receive premedication, statistically significant differences were observed, specifically between neonates and geriatric patients ($p=0.001$), between paediatric and geriatric patients ($p=0.0005$),

Table 10. Descriptive statistics of cats that received an a_2-agonist based premedication protocol in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) divided by indication for anaesthesia.

α_2-Agonists						
Indication for anaesthesia	N	Propofol (mg/kg b.w.)			Kruskal-Wallis Test	
		Median |	Min	Max	X^2	Significance (Monte Carlo)
Radiographic Examinations	137	2.50	0.77	15.63		
Soft Tissue Surgery	170	2.14	0.32	15.00		
Spinal Surgery	5	3.33	1.11	10.00		
Dentistry	84	2.46	0.79	10.77	11.025	0.051
Orthopedic Surgery	53	3.00	0.58	5.56		
Ophthalmic Surgery	15	1.85	1.00	4.00		
Total	464					

Table 11. Descriptive statistics of dogs that received a non a_2-agonist based premedication protocol (other drugs) in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) divided by indication for anaesthesia.

OTHER DRUGS						
Indication for anaesthesia	N	Propofol (mg/kg b.w.)			Kruskal-Wallis Test	
		Median	Min	Max	X^2	Significance (Monte Carlo)
Radiographic Examinations	145	2.67	0.41	11.63		
Soft Tissue Surgery	343	2.72	0.24	14.00		
Spinal Surgery	27	4.00	1.00	12.00		
Dentistry	82	2.83	0.88	16.67	13.868	0.016
Orthopedic Surgery	82	2.92	0.91	5.75		
Ophthalmic Surgery	19	2.94	1.32	15.22		
Total	698					

Table 12. Descriptive statistics of cats that received a non a_2-agonist based premedication protocol (other drugs) in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) divided by indication for anaesthesia.

OTHER DRUGS						
Indication for anaesthesia	N	Propofol (mg/kg b.w.)			Kruskal-Wallis Test	
		Median	Min	Max	X^2	Significance (Monte Carlo)
Radiographic Examinations	27	5.00	2.00	34.00		
Soft Tissue Surgery	87	2.94	1.00	14.29	11.771	0.001
Ophthalmic Surgery	1					
Total	464					

Table 13. Descriptive statistics of dogs that did not receive any premedication in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) allocated into groups according to age.

NO PREMEDICATION						
Age	**N**	**Propofol (mg/kg b.w.)**			**Kruskal-Wallis Test**	
		Median	**Min**	**Max**	**X^2**	**Significance (Monte Carlo)**
Neonates	5	6.25	3.04	14.44		
Paediatric	6	6.01	5	13.64		
Adults	54	3.82	0.97	13.85	23.368	**<0.0005**
Geriatric	34	2	1	12.04		

and between adult and geriatric patients (p=0.001). Corresponding results for cats are shown in table 14, where statistically significant differences were observed between neonates and adults (p=0.005) and between paediatric and adult patients (p=0.002). In all cases, the geriatric groups required lower doses of propofol.

In the group of dogs that received an α_2-agonist (with or without other drugs) as premedication, statistically significant differences were observed in the dose of propofol required for anaesthesia induction among all age groups except between neonates and paediatric patients, as shown in table 15. Specifically, statistically significant differences were observed in the dose of propofol required for anaesthesia induction between neonates and adults (p=0.0005), neonates and geriatric patients (p=0.0005), paediatric patients and adults (p=0.0005), paediatric patients and geriatric patients (p=0.0005), and adults and geriatric patients (p=0.0005).

In the group of cats that received an α_2-agonist (with or without other drugs) as premedication, sta-

Table 14. Descriptive statistics of cats that did not receive any premedication in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) allocated into groups according to age.

NO PREMEDICATION						
Age	**N**	**Propofol (mg/kg b.w.)**			**Kruskal-Wallis Test**	
		Median	**Min**	**Max**	**X^2**	**Significance (Monte Carlo)**
Neonates	2	27.5	25	30		
Paediatric	4	12.14	6	20		
Adults	18	4.14	2	6.9	14.808	**<0.0005**
Geriatric	3	2	1	3.7		

Table 15. Descriptive statistics of dogs that received an a_2-agonist based premedication protocol in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) allocated into groups according to age.

α_2-Agonist						
Age	**N**	**Propofol (mg/kg b.w.)**			**Kruskal-Wallis Test**	
		Median	**Min**	**Max**	**X^2**	**Significance (Monte Carlo)**
Neonates	9	4.28	2.22	9.76		
Paediatric	189	3.8	1	15.38		
Adults	1938	2.1	0.24	18.6	391.872	**<0.0005**
Geriatric	333	1.61	0.2	5.88		

tistically significant differences were observed in the dose of propofol required for anaesthesia induction among all age groups, as shown in table 16. Specifically, statistically significant differences were observed between neonates and paediatric patients (p=0.001), between neonates and adults (p=0.0005), between neonates and geriatric patients (p=0.0005), between paediatric patients and adults (p=0.0005), between paediatric patients and geriatric (p=0.0005), and finally, between adults and geriatric patients (p=0.0005). In all cases, the geriatric groups required lower doses of propofol.

In the group of dogs that received other drugs as premedication, statistically significant differences were observed in the dose of propofol required for anaesthesia induction among all age groups except between neonates and paediatric patients, as shown in table 17. Specifically, statistically significant differences were observed in the dose of propofol required for anaesthesia induction between neonates and adults (p=0.0005), neonates and geriatric patients (p=0.0005), paediatric patients and adults (p=0.0005), paediatric patients and geriatric patients (p=0.0005), and adults and geriatric patients (p=0.0005).

In the group of cats that received other drugs as premedication, statistically significant differences were observed in the dose of propofol required for anaesthesia induction among all age groups except between and paediatric patients, as shown in table 18. Specifically, statistically significant differences were observed in the dose of propofol required for anaesthesia induction between neonates and adults (p=0.0005), between neonates and geriatric patients (p=0.0005), between paediatric patients and adults (p=0.0005), between paediatric patients and geriatric patients (p=0.0005), and finally, between adults and geriatric patients (p=0.0005). In all cases, the geriatric groups required lower doses of propofol.

DISCUSSION

The purpose of this retrospective study was to examine if the neonates and paediatric patients have lower propofol requirements for induction of anaesthesia compared to adults is true, while geriatric patients require less, as mentioned in the literature. The findings of the study reject the null hypothesis regarding paediatric patients and confirm the null hypothesis regarding geriatric patients.

In the present study, there were no statistically

Table 16. Descriptive statistics of cats that received an a_2-agonist based premedication protocol in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) allocated into groups according to age.

α_2-Agonist						
Age	**N**	**Propofol (mg/kg b.w.)**			**Kruskal-Wallis Test**	
		Median	**Min**	**Max**	**X^2**	**Significance (Monte Carlo)**
Neonates	5	10	7	14		
Paediatric	50	4.22	1.76	15.63		
Adults	365	2.22	0.58	6.67	112.956	**<0.0005**
Geriatric	44	1.87	0.32	3		

Table 17. Descriptive statistics of dogs that received a non a_2-agonist based premedication protocol (other drugs) in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) allocated into groups according to age.

OTHER DRUGS						
Age	**N**	**Propofol (mg/kg b.w.)**			**Kruskal-Wallis Test**	
		Median	**Min**	**Max**	**X^2**	**Significance (Monte Carlo)**
Neonates	27	5.71	2.88	16.67		
Paediatric	50	5.12	2.35	14		
Adults	353	2.92	0.24	15.22	151.447	**<0.0005**
Geriatric	268	2	0.38	9.38		

Table 18. Descriptive statistics of cats that received a non a_2-agonist based premedication protocol (other drugs) in which induction of anaesthesia was carried out with propofol (IV dose in mg/kg b.w.) allocated into groups according to age.

OTHER DRUGS						
Age	**N**	**Propofol (mg/kg b.w.)**			**Kruskal-Wallis Test**	
		Median	**Min**	**Max**	**X^2**	**Significance (Monte Carlo)**
Neonates	8	9.71	4	34		
Paediatric	14	8.47	5	14.29		
Adults	69	3.2	1	8.33	67.114	**<0.0005**
Geriatric	24	1.95	1	2.94		

significant differences between either dogs or cats regarding sex. In veterinary medicine, no study has reported data on the dose of propofol required for anaesthesia induction concerning patients' sex. In a relevant study conducted in humans, statistically not significant differences were found in the amount of propofol required (Kodaka et al., 2005), while other studies suggest that women awaken faster than men when anesthetized with propofol and require larger amounts of propofol than men for anaesthesia induction (Pleym et al., 2003; Vuyk et al., 2001). This is attributed to pharmacokinetic and pharmacodynamic differences, as well as differences in sensitivity to propofol between the two sexs, according to the authors (Gan et al., 1999; Hoymork and Raeder, 2005).

Statistically significant differences were found between most age groups regarding the required dose of propofol, except for the comparison between neonates and paediatric patients. These results reject the null hypothesis that young animals (neonates and paediatrics) require a lower dose of propofol for anaesthesia induction than adults and confirm the null hypothesis that geriatric animals require a lower dose of propofol than adults.

No studies were found in the veterinary small animal literature investigating the required dose of propofol for induction of anaesthesia in neonates and paediatric patients. In human medicine, younger patients have a higher minimum alveolar concentration (MAC) when compared to adults(Eger, 2001); paediatric patients require higher doses of propofol compared to adults due to differences in volume of distribution, clearance, and cardiac output (Jasiak et al., 2012). In rats, younger animals need larger propofol doses for induction of anaesthesia when compared to older animals(Larsson and Wahlström, 1998).

For geriatric patients, there is more data in both veterinary and human literature. The finding of this study, that geriatric animals have lower propofol requirements, is confirmed by other researchers (Reid, 1996). The same conclusions are also found in human medicine (Eleveld et al., 2014; Jia et al., 2020). In both geriatric humans and animals, propofol exhibits prolonged clearance and altered pharmacokinetics, due to increased fat and reduced water in the patients' bodies and potential organ dysfunction (Jia et al., 2020; Reid, 1996). However, it is debatable whether such pharmacokinetic alterations should be held accountable for the reported decreased requirements, since cessation of anaesthetic action of propofol for induction is via redistribution of the drug to body tissues. In a recent retrospective study, researchers were not able to associate absolute or physiologic age with a reduction in the dose of administered propofol during induction of anaesthesia(Hampton et al., 2023). A reduction was associated statistically with percentage of elapsed life expectancy (considering each breed's life expectancy) but to such a small degree that would not consist of a clinically relevant effect. Our study's cohort consisted of a large population of mixed breed dogs (almost 45% of the total population) so such a calculation could not be performed.

Significant statistical differences were found in the required propofol dose between specific groups regarding the indications for anaesthesia. One consistent finding was that higher doses of propofol were required in dogs in the spinal surgery group. No study has been reported in the literature so far, either in humans or animals, regarding the need for higher amounts of propofol in spinal surgery. A possible explanation for this result could be the pain associated with spinal surgery cases (Olby et al., 2020), which may not be present or as intense in other cases.

In cats allocated to the group that received other drugs, a statistically significant difference was found between the radiographic/diagnostics group and the soft tissue surgery group. In some animals of the radiographic diagnostics group, a very high dose of propofol was recorded (e.g., 34 mg/kg b.w. b.w.). Such values indicate a possible error in noting the total amount of propofol administered throughout the diagnostic procedures (maintenance of anaesthesia with propofol) or a possible decimal error. These outlier values have likely affected the results of the entire radiographic/diagnostics group, as the group consisted of only eight animals, resulting in a potentially false statistically significant difference compared to the soft tissue surgeries group.

The only group where the results were slightly different was the dogs receiving no pre-anaesthetic medication. The small number of dogs that were included in this group could be the reason why significant differences were not detected among the other age sub-groups in the no premedication animals.

In all age groups, animals without pre-anaesthetic medication required a higher dose of propofol for induction compared to animals premedicated with α_2-agonists and to animals premedicated with other drugs. The same conclusions also arise from other studies. One study reports that the propofol dose required for anaesthesia induction without pre-anaesthetic medication is 6 mg/kg b.w. (Hammond and England, 1994), with similar results found in another study with a propofol dose of 5.2 +/- 2.3 mg/kg b.w. in dogs and 5.0 +/- 2.8 mg/kg b.w. in cats (Weaver and Raptopoulos, 1990). The authors in that study report that the propofol dose after pre-anaesthetic medication with other sedatives/analgesics except α_2-agonists is 3.6 +/- 1.4 mg/kg b.w. in dogs and 5.3 +/- 4.3 mg/kg b.w. in cats (Weaver and Raptopoulos, 1990), while the propofol dose with pre-anaesthetic medication with an α_2-agonist ranges from 0.9 mg/kg b.w. to 3 mg/kg b.w. depending on the α_2-agonist dose (Hammond and England, 1994). A direct comparison between the a_2-agonist and "other drugs" premedication category was not performed as it was not in the scope of this study to identify the effect that different premedicants have on propofol requirements for induction.

For the present study, the authors identify several limitations. The retrospective nature of the study, having to rely on data recorded on anaesthetic records, could potentially lead to false conclusions especially in groups with a small number of patients. A characteristic example seems to be a case in the group of neonatal cats that according to the anaesthetic record received other drugs as pre-anaesthetic medication and was administered propofol at a dose of 34 mg/kg b.w., likely recorded incorrectly, as the dose is too high to have been administered for anaesthesia induction.

On the same note, regarding the animals allocated on the "other drugs" category, an individual analysis of each different premedicant was not performed. Different premedicants could influence the propofol requirements differently and thus, influencing the results. To minimize this, we only made comparisons regarding age groups within each premedication category and avoided comparisons between groups.

Another limitation is the number of animals, which, while large overall, is small in specific age groups. Specifically, while there is a large enough number of animals in the adult group, the paediatric and geriatric groups have substantially fewer animals, and in the neonate group, the number of animals is very small. It is possible that for certain statistical tests that did not yield significant results in these age groups, statistically significant results might have emerged if the numbers of animals in these groups were higher.

This study has another limitation; the findings might have been affected by the neutering status of the patients. A study comparing the effect of gonadectomy on pain intensity in dogs after stifle surgery found that neutered female and castrated male dogs exhibited lower pain thresholds (Karamichali et al., 2023). Further research is needed to address the issue of sex and neutering status affecting propofol requirements on induction

Finally, the lack of standardization of the speed of injection of propofol for induction can be considered another limitation of the study. In our clinic, it is standard practice to administer propofol for anaesthesia induction "to effect," with doses of 0.5-1 mg/kg b.w. at a time and with a time interval of approximately one minute separating one dose from the next one until tracheal intubation can be easily achieved. Therefore, the smallest effective possible dose is administered by default. If a direct bolus of propofol was given in relatively large doses, more propofol might have been administered than necessary for unhindered tracheal intubation compared to the case in which propofol was given "to effect."

Similarly, criteria for unhindered intubation are

judged by different vets and students, and appropriate anaesthetic depth can be challenging to standardize. The aim for tracheal intubation to be achieved in our clinic is that of a smooth induction with absence of cough, swallow and/or gagging by the patient. The authors believe that this could also be a factor for the variance of induction dose among groups.

The retrospective nature of the study precluded attempts for standardization of the speed of injection of propofol for induction.

CONCLUSIONS

In conclusion, according to the findings of the present study neonates and paediatric patients require significantly higher doses of propofol for induction of anaesthesia in both dogs and cats compared to adult animals, while geriatric patients require significantly lower doses of propofol for induction of anaesthesia in both dogs and cats compared to adult animals. Neonates and paediatric patients require significantly higher doses of propofol for induction of anaesthesia in both dogs and cats compared to geriatric patients. To our knowledge this is the first study to examine this particular subject in dogs and cats.

When propofol is used for anaesthetic induction, animal age should be factored in, and dosing adjusted accordingly.

Author Contributions

Conceptualization, T.A. and K.G.; methodology, T.A.; software, I.S..; validation, T.A., V.Z.; formal analysis, I.S., T.A.; investigation, V.Z.,V.K.,I.T.,K.G..; data curation, V.Z., V.K., I.T.; writing—original draft preparation, V.Z., K.G..; writing—review and editing, V.Z., T.A., V.K., P.L., K.G.; visualization, P.L., I.S., K.G.; supervision, T.A.,K.G.; project administration, P.L., T.A. All authors have read and agreed to the published version of the manuscript."

Data Availability Statement

The anaesthetic records that were used for this study can be found in the anaesthesiology and icu department's archive, Stavrou Voutura 11, Thessaloniki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Informed Consent Statement

Informed consent to use patient information for retrospective studies in our institute is obtained with the anaesthetic and procedural consent form on patient admission.

Abbreviations

The following abbreviations are used in this manuscript:

GABA	gamma-aminobutyric acid
A.U.TH.	Aristotle University of Thessaloniki
IV	Intravenous
MAC	Minimum alveolar concentration

APPENDIX A

Table A.1 Number of dogs included in the study divided by breed.

Breed	n	Breed	n
Airedale Terrier	3	Husky	30
Akita	21	Jack Russell	39
American Staffordshire	7	Kangal	1
Asian Shepherd	12	Kokoni	14
Basset Hound	1	Kurzhaar	7
Beagle	31	Labrador	95
Bichon Frise	1	Lagotto Romagnolo	1
Blood Hound	1	Malinois	20
Bobtail	4	Maltese	143
Boston Terrier	5	Mastino Napolitano	1
Boxer	72	Mixed breed	1471
Brittany Spaniel	8	NewFoundland	3
Bull Mastiff	2	Papillon	5
Bull Terrier	15	Pekignese	55
Canadian Shepherd	4	Pincher	61
Cane Corso	28	Pitbull	76
Cavalier King Charles	14	Pointer	17
Caucasian	10	Pomeranian	31
Chihuahua	23	Poodle	64
Chow Chow	15	Presa Canario	4
Cocker Spaniel	61	Pug	30
Collie	17	Rhodesian Ridgeback	3
Dachshund	13	Rottweiler	61
Dalmatian	5	Saint Bernard	2
Doberman	31	Samoyed	4
Dogo Argentino	19	Schnauzer	6
English Bulldog	22	Segugio Italiano	2
Fox Terrier	9	Setter	45
French Bulldog	73	Shar-pei	11
German Shepherd	140	Shihtzu	27
Golden Retriever	31	Spitz	13
Greek Harehound (Gekas)	41	Springer Spaniel	1
Greek shepherd	20	Vizsla	1
Greyhound	1	West Highland terrier	32
Great Dane	6	Yorkshire terrier	119
Griffon	5	total	3266

Table A.2. Number of cats included in the study by breed.

Breed	n
Birman	2
British Shorthair	1
Domestic Long-haired Cat	7
Domestic Short-haired Cat	552
Maine Coon	5
Persian	19
Ragdoll	2
Russian Blue	3
Scottish fold	3
Siamese	9
Siberian	1
Sphynx	1
Turkish Angora	1
Total	606

Table A.3. Number of dogs included in the study by sex.

Sex	n Number of dogs
Male	1698
Female	1568
Total	3266

Table A.4. Number of cats included in the study by sex.

Sex	n Number of cats
Male	302
Female	304
Total	606

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