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Evaluating the efficiency of different propofol doses associated with age and gender in rats

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ABSTRACT

Aim: To investigate the effect of different intraperitoneal (IP) doses of propofol on the duration and depth of anesthesia according to age and gender.

Method: The rats were divided into three main groups according to propofol dose (GI: 5 mg/kg, GII: 10 mg/kg and GIII: 15 mg/kg). These three groups were divided into two subgroups as male and female. (M: Male, F: Female). Male and female groups in each dose group were divided into five different sub-age groups: 1: 2-6 months (0-12 years = Childhood), 2: 7-12 months (12-18 years = Adolescent), 3: 13-18 months (30-45 years = Young adult), 4: 19-24 months (45-60 years = Adult) and 5: older than 25 months (65 years old = Elderly). The duration and depth of anesthesia in different ages and genders were compared statistically.

Results: There were differences with regard to the palpebral, pinch, corneal and muscle tone reflexes at propofol administration doses of 5 mg/kg (GI), 10 mg/kg (GII) and 15 mg/kg (GIII) in different ages and genders (Table 1). We detected that 50 minutes of deep anesthesia was achieved with a dose of 10 mg/kg up to 18 months and older than 24 months male rats. A dose of 10 mg/kg was sufficient for short-term (20-minute deep anesthesia) procedures in male rats aged 19-24 months. We detected that 50 minutes of deep anesthesia was achieved with a dose of 15 mg/kg in 7-12 and 13-18 month old female rats. A dose of 10 mg/kg dose was sufficient for short-term procedures in 0-6 month old female rats. However, only superficial anesthesia was detected at the dose of 15 mg/kg in female rats older than 18 months.

Conclusion: The present study demonstrated that 10 or 15 mg/kg low doses of intraperitoneal propofol administration affected the duration and depth of anesthesia in different ages and genders in rats.

Key words: Propofol, rat, intraperitoneal, anesthesia, gender.

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Introduction

Anesthesia protocols are crucially important in experimental animal studies. Selection of the anesthetic agent and its dose is dependent on many factors, including purpose of the experiment, type and duration of the surgical procedure, and researcher's experience as well as

the animal's breed and age. The success of the experimental study is positively associated with the selected anesthetic agent, its administration route and dose. An ideal anesthetic agent should have a rapid onset of action, should not have any toxic effects on organs and tissues, and should be able to provide rapid awakening and recovery as soon as anesthesia is terminated [1, 2]. Therefore, anesthesia protocols, which provide a rapid onset of action and a sufficient surgical time and rapid recovery, are preferred.

In experimental animal studies, different anesthetic agents (e.g. propofol, barbiturates, medetomidine, and ketamine-xylasin) can be administered in different routes, such as intraperitoneal (IP), intravenous (IV) and intramuscular (IM). Inhalation anesthetics are frequently used in animal studies. However, lack of sufficient equipment or inability to use nasopharyngeal procedures is the main disadvantages of inhalation anesthesia [3, 4]. Moreover, late onset of action, short acting duration and gas exposure to the researchers due to the gas let off from the operation chamber also restricts its uses [5]. Recently, intravenous anesthetics have gained more popularity due to their rapid onset of action, longer efficiency duration and their ease of use [3].

Propofol is one of the most preferred modern induction agents and provides a rapid onset of action and deep anesthesia level as well as a short duration of sleep time. Propofol, which belongs to alkylphenol group with a chemical formula of 2,6-diisopropylphenol, was first clinically used in 1977 [6]. However, its mechanism of action is not fully known. It might primarily act through reducing the dissociation of GABA from its receptors. Alternatively, it could exert its effects acting through sodium, potassium, cholinergic and NMDA receptors. Its metabolism could be changed by a dose dependent inhibition of cytochrome p-450. Its pharmacokinetics are directly associated with gender, body weight, chronic diseases, age and medicines used. The distribution volume and clearance are high in women and babies. However, the elimination half-life is the same between men and women. On the other hand, the elderly have shown a decreased distribution volume and clearance to the drug. Central distribution volume and elimination time are increased in liver patients, but there has been no difference reported for clearance. Propofol is inactivated via conjugation in the liver through metabolization into glucuronite and sulfates [1, 7]. It can lead to various complications, including hypotension, hypoxemia, hypercapnia, bradycardia, asystole, and respiratory acidosis [8, 9]. Despite its complications and disadvantages, propofol is frequently used in induction or short-term anesthesia in experimental animal studies at varying doses [10].

The impact of the route of propofol administration and dose on the depth and quality of anesthesia is not well understood. There is a lack of consensus on the most effective dose and route of administration in experimental animal studies. The main aim in choosing such agents is to provide the highest anesthesia depth at the lowest doses. An unnecessarily high dose of anesthetic agents could adversely affect the study and lead to ethical violations. Moreover, it could also lead to an increase in the unnecessary drug consumption. In the literature, administration of higher doses of propofol alone or in combination with other agents (50, 75, 100 and 200 mg/kg body weight) has been reported. However, the results were controversial [3]. The route of propofol administration could affect the dose selection. Previous studies suggested that IP administration at lower doses could provide more efficient and sufficient anesthetic depth.

The aim of the present study was to evaluate the impact of age and gender on the anesthesia depth and duration of IP administered propofol at lower doses in rats. Moreover, it was also aimed to determine the most efficient anesthetic doses.

Materials and methods

The present study was designed to determine the impact of age and gender on the efficiency of propofol at various doses. Therefore, the current study was conducted on male and female albino Wistar rats obtained from Bolu Abant Izzet Baysal University (BAIBU) Experimental Animals Application and Research Center. The experiments were conducted following the approval by the BAIBU Animal Research Local Ethical Committee with a date of November 13, 2015 and numbered of 2015/48.

Obtaining of experimental animals and the study groups

The experimental animals were obtained from BAIBU Experimental Animals Application and Research Center. Prior to and throughout the experiments, all animals were kept at the same room with 12 hour light: dark cycle and 60-70% relative humidity. Food and water were provided *ad libitum*.

The study was completed with 240 rats, 120 male and 120 female with a randomized double-blind method. The rats were divided into three main groups according to propofol dose (GI: 5 mg/kg, GII: 10 mg/kg and GIII: 15 mg/kg). These three groups were divided into two subgroups as male and female. (M: Male, F: Female). Male and female groups in each dose group were divided into five different sub-age groups: 1: 2-6 months (0-12 years = Childhood), 2: 7-12 months (12-18 years = Adolescent), 3: 13-18 months (30-45 years = Young adult), 4: 19-24 months (45-60 years = Adult) and 5: older than 25 months (65 years old = Elderly) (Figure 1). The drugs were given intraperitoneally (ip). Intraperitoneal administration was performed by an experienced investigator from the right paramedian line at a 45-degree angle in the ventral position.

For the present study, age ranges of rats were determined through comparing the average age of rats with that of humans based on the previously published data from Robert Quinn [11] and Sengupta [12]. To do this, average age of rats were assumed as 3 years. Likewise, an average human age was assumed as 80 years (26.7 human day =1 rat day, and 13.7 rat day = 1 human year). The above equation and assumptions were used to determine age ranges and groups for the present study.

Determination of the anesthetic agent doses

The amount of the propofol administration was determined based on the most frequently used dose (10 mg/kg body weight) in routine applications [13, 14]. Half of the routine dose (5 mg/kg body weight) and 1.5 times of that dose (15 mg/kg body weight) were administered IP in three experimental groups.

Determination of the depth of the anesthesia

The efficiency and depth of the anesthetic agent were evaluated at 1, 5, 10, 20, 30, 40, 50 and 60 min following the administration of propofol through measurement of the palpebral reflex, pinching reflex, corneal reflex and muscle tone (by pulling the lower jaw or extremities).

While anesthesia deepened, scoring was done as follows:

1. Superficial anesthesia if the eyelids wink with touch (Palpebral reflex).
2. Superficial anesthesia if the animal pulls the toe with pinching (Pedal reflex).
3. Deep anesthesia if the animal does not blink with touch with cotton or thread (DA; Corneal reflex).

4. Deep anesthesia if there is no pull in the lower jaw or extremities (Jaw Ton).

Anesthesia exit duration (AE) was determined observing the absence of these reflexes [15]. determined as the entry moment to the superficial anesthesia (SA), entry moment to the deep anesthesia (DA), and exit moment of the anesthesia (AE) and are represented in Table 2.

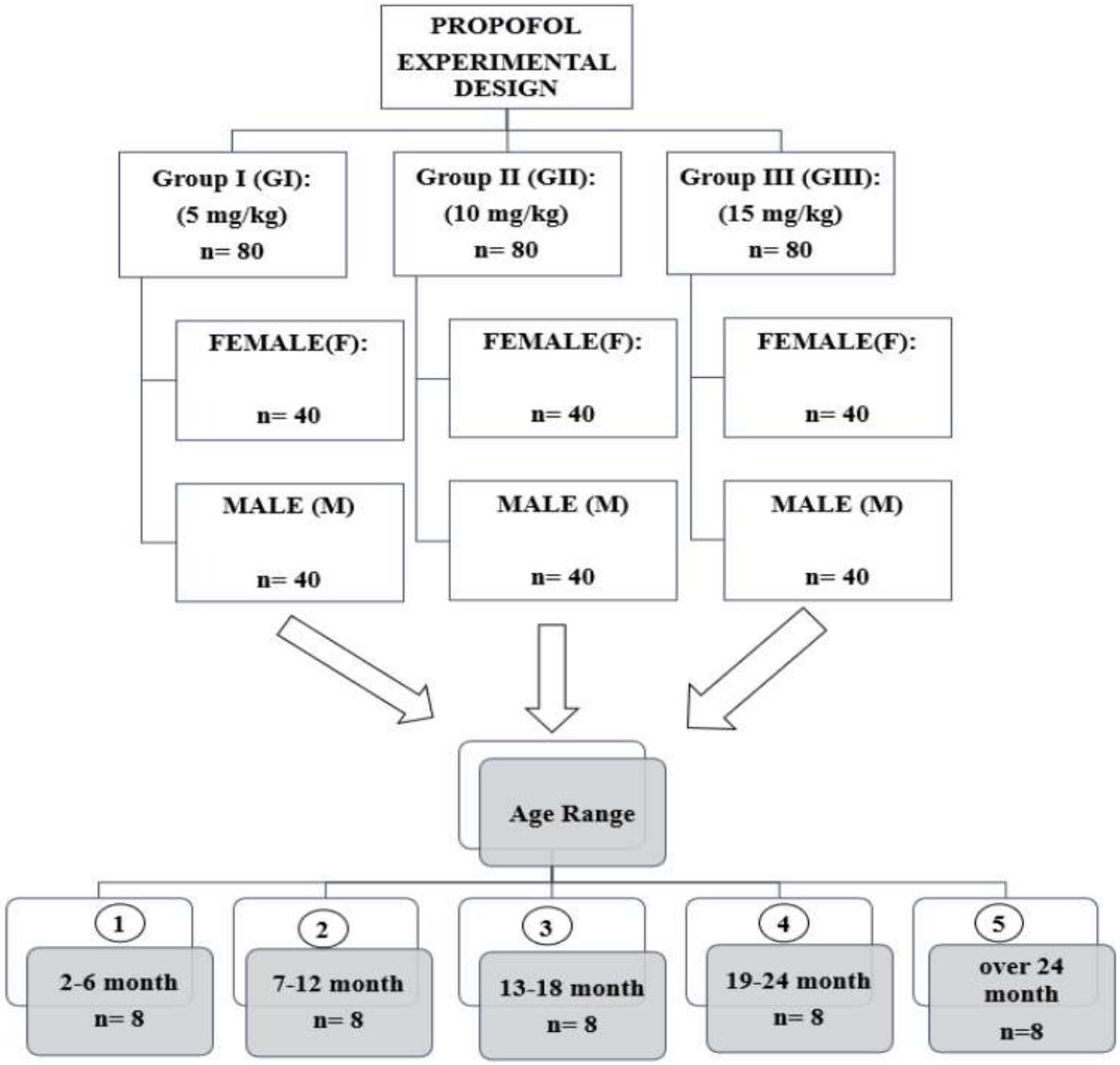

Figure 1. Propofol experimental design

Results

Propofol was IP administered to the rats in five different age groups (0-6 months, 7-12 months, 13-18 months, 19-24 months, and 24 months and over) as three different doses (5, 10 and 15 mg/kg body weight) (Figure 1). The depth of anesthesia was evaluated through measurement of the muscle tone, pinching reflex, corneal reflex and palpebral (Table 1). The depth of anesthesia was

Evaluating the impact of age in male rats on the administered doses

Administration of 10 and 15 mg/kg body weight of propofol in male rats at 0-6 months, 7-12 months, and 13-18 months of age resulted in the entry of deep anesthesia at 10 min and 50 min duration of total anesthesia. However, in 19-24 months of age male rats, entry to the superficial anesthesia at 10 min and 50 min of total

Table 1. Evaluating different propofol doses on particular reflexes in different age groups of rats on both sexes.

Age	Reflexes	Female			Male		
		5 mg/kg Propofol ip	10 mg/kg Propofol ip	15 mg/kg Propofol ip	5 mg/kg Propofol ip	10 mg/kg Propofol ip	15 mg/kg Propofol ip
0-6 months	PR	-	+	-	-	-	-
	PER	-	-	+	-	-	-
	CR	-	+	-	-	-	-
	JT	-	-	+	-	-	-
7-12 months	PR	+	-	+	+	+	+
	PER	+	-	+	+	-	+
	CR	+	+	-	+	-	+
	JT	+	-	+	+	-	+
13-18 months	PR	-	+	+	+	+	+
	PER	-	+	+	+	+	+
	CR	+	+	+	-	-	+
	JT	+	-	+	+	-	+
19-24 months	PR	+	+	-	-	-	-
	PER	+	-	-	+	-	+
	CR	+	+	-	-	-	-
	JT	-	-	-	+	-	+
24 months and over	PR	+	-	+	-	-	-
	PER	-	-	+	-	-	-
	CR	+	+	+	-	-	-
	JT	-	-	+	-	-	-

anesthesia duration were only observed at 5 mg/kg body weight of propofol administration. In male rats of 24 months of age and over, 5 mg/kg body weight of IP propofol administration resulted in 50 min superficial anesthesia depth. Likewise, in the same group, 10 mg/kg body weight of IP propofol administration caused 50 min of deep anesthesia duration (Table 2).

Evaluating the impact of age in female rats on the administered doses

At 0-6 months of age females, 10 min of deep anesthesia duration and 25 min of superficial aesthesia duration was observed following 10 mg/kg body weight of IP propofol administration. On the other hand, only 55 min of superficial anesthesia duration was observed in 15 mg/kg body weight of propofol administration group. At 7-12 months of age, 50 min of superficial anesthesia and 40 min of deep anesthesia were observed in 5 mg/kg body weight of propofol administration group. Likewise, 25 min of superficial anesthesia and 20 min of deep anesthesia were observed in 10 mg/kg body weight group. 55 min of superficial anesthesia and 50 min of deep anesthesia were observed in 15 mg/kg body weight group. At 13-18 months of age, 5 mg/kg body weight of propofol administration resulted in a 50 min duration of superficial anesthesia. However, no

deep anesthesia was observed in this group. 55 min of superficial anesthesia and 50 min of deep anesthesia were observed in both 10 and 15 mg/kg body weight of propofol administration groups. At 19-24 months of age, all three propofol administration doses resulted in 55 min duration of superficial anesthesia without a deep anesthesia. At 24 months of age and over, 10 min duration of deep anesthesia in 5 mg/kg body weight, 25 min duration of superficial anesthesia in 10 mg/kg body weight, and 55 min duration of superficial anesthesia in 15 mg/kg body weight of propofol administration were observed (Table 2).

Table 2. Effect of propofol doses on anesthesia depth in different age range rats.

Age	Female									Male								
	5 mg/kg ip			10 mg/kg ip			15 mg/kg ip			5 mg/kg ip			10 mg/kg ip			15 mg/kg ip		
	SA* (dk)	DA* (dk)	RA* (dk)	SA* (dk)	DA* (dk)	RA* (dk)	SA* (dk)	DA* (dk)	RA* (dk)	SA* (dk)	DA* (dk)	RA* (dk)	SA* (dk)	DA* (dk)	RA* (dk)	SA* (dk)	DA* (dk)	RA* (dk)
0-6 Month	-	-	-	5.	20.	30.	5.	-	60.	-	-	-	-	10.	60.	-	10.	60.
7-12 Month	10	20.	60.	5.	10.	30.	5.	10.	60.	-	-	-	-	10.	60.	-	10.	60.
13-18 Month	10	-	60.	5.	10.	60.	5.	10.	60.	-	-	-	-	10.	60.	-	10.	60.
19-24 Month	5	-	60.	5.	-	60.	5.	-	60.	10.	-	60.	5.	20.	30.	-	-	-
Over 24 Month		20.	30.	5.	-	30.	5.	-	60.	10.	-	60.	-	10.	60.	-	10.	20.

SA*: Entry minute o superficial anesthesia, DA*: Entry minute o deep anesthesia , RA*: Recovery from anesthesia

Discussion

In experimental animal studies, choosing an appropriate anesthetic agent and dose based on the animals' age, gender and species is not only crucially important for the quality of study, but also important for ethical consideration. It is known that the effects of many anesthetic agents may vary depending on gender and age [16]. Rats are frequently preferred models in experimental animal studies since the similar physiological conditions of human beings can be mimicked [17]. Anesthetic agents are often administered intraperitoneally in rats. Therefore, propofol is commonly used for induction and short-term procedures in animal studies. Independent of the administered dose, waking up from propofol anesthesia is typically fast and with little or no complications [8, 9, 18]. It has been reported that propofol can be administered at different doses and routes. Even though it is commonly administered through IV, many studies have reported using IM and IP administration [3, 19, 20]. However, less is known about the impact of age and gender on the dose dependent anesthesia depth and duration efficiency of IP propofol administration. Alves HC et al. examined single IP administration of 50, 75, 100 and 200 mg/kg body weight of propofol in rats. Moreover, they also co-administered it with fentanyl, sufentanyl and remifentanyl and reported inconsistent results in all groups tested. They determined that 200 mg/kg body weight dose was an ideal dose because it caused a loss of light reflex in every 3 out of 4 tested animals.

Induction time was reported as 4±1, 5 and 4±1 min in 75, 100 and 200 mg/kg body weight dose administration, respectively. Sleeping time was

reported as 10, 15 and 24±1 min. In the same study, they reported that IP propofol administration did not provide sufficient hypnotic level [20]. In another study of Alves et al. propofol was IP co-administered with medetomidine and fentanyl. First, they did a preliminary study using propofol alone at doses of 50,100,150, and 200 mg/kg. They reported that the most appropriate dose for IP was 200 mg/kg because it induced a loss of light reflex in 3 out of 4 animals tested but other doses were insufficient to induce anesthesia [3]. In the study of Yasuda et al., where they tested the hypothesis of reduced of anesthesia duration through TNF-α with the induction of propofol and ketamine, the anesthesia sleep time was determined as 43.5±11.0 min [21]. In the present study, lower IP propofol doses (5, 10 and 15 mg/kg body weight) induced anesthesia depth at different age groups. Moreover, the depth and efficiency of anesthesia were dose-dependently increased in female at older age compared to the males. Even though there were inter group differences, anesthesia onset time was approximately 5 min in females and 10 min in males following 10 mg/kg body weight propofol administration. Total anesthesia duration was 30 min in 0-13 months and 24 months and over age group females. Likewise, it was approximately 60 min in 0-19 months and 24 months and over age group males.

The large omentum surface and intraabdominal organs facilitate the absorption of hydrophobic drugs in intraperitoneal administration. In this way, the drugs are absorbed by the portal system and undergo a significant first pass hepatic metabolism. Moreover, gastrointestinal and extraperitoneal drug loss is also present. As a result, the minimum drug concentration that provides adequate anesthesia induction may differ based on the age and gender [22, 23]. In the study of Simons et al., the distribution of propofol at anesthetic doses in female rats was investigated and depending on its lipophilic properties, it was reported that there was a fast distribution throughout the body following an IV administration. Moreover, they also showed that it could be cleared from the body through metabolism; however, its clearance rate in adipose tissue was reported to be slow. They reported that the short-term effect of high doses of propofol could be caused by the re-release of the drug by adipose tissue and being cleared through metabolism [19]. Consistent with these data, the results of the present study also suggested a dose and age dependent decrease of reflexes in females compared to the males.

Propofol has no clinical intraperitoneal use in humans. The long elimination half-life of propofol is associated with its slow release from high lipophilic tissues, such as fat [13]. Dahaba's et al., 80 patients were divided into 8 different age groups at 10-year intervals (20-29 years to 90-99 years). Using target-controlled infusion (TCI) and electroencephalographic (EEG) - derived bispectral index (BIS), they adjusted the plasma concentration (Cp) of the propofol to gradually reach 3.5 mg / mL for 3.5 minutes. As a result of this simulation model, while the plasma concentration recommended to reach BIS 50 is 3.5 mg / mL at 20-29 years of age, this value was reported to be 3.0 mg/ml at the age of 30-49, 2.5 mg/ml at the age of 50-69 and 2.0 mg/ml at the age of 80-89. The results of that study suggested that with an increased age less anesthetic agents are required, and, therefore, dose re-adjustment may be required. Moreover, different anesthesia onset and duration were reported in various age groups tested with different doses of anesthetic agents [24]. The effects of IP administrated propofol were associated with age and gender in our study. Depending on the content of the study,

superficial or deep anesthesia is preferred in animal experiments. We detected different anesthesia levels at various age and dose groups in our study.

There were some limitations of the present study. There was a lack of evaluation of propofol blood concentration following its administration. Instead of determining surgical anesthesia duration, only sleeping time was examined. Changes in cardiac and respiratory parameters associated with the depth of anesthesia were not recorded. And lastly, in the present study, anesthesia depth of male and female rats in different ages groups following only IP administration of various doses of propofol (5, 10 and 15 mg/kg body weight) under normal circumstances were evaluated.

In conclusion, the IP administration of anesthetic agents provides an ease of use in experimental animal studies. Selection of an appropriate dose of anesthetic agents based on age and gender could ensure an on-time termination of experimental studies. Moreover, it also provides compliance to the ethical rules without harming the animals throughout the conduction of experiments. As a result, the data can be collected in an accurate and scientific manner. More comprehensive future studies are required to investigate the duration and depth of surgical anesthesia associated with age and gender. The results of the present study suggest that in male rats; A dose of 10 mg/kg may be preferred for a deep anesthesia period of approximately 50 minutes for up to 18 months and over 24 months. A dose of 10 mg/kg may be preferred for short-term (20-minute deep anesthesia) procedures in rats aged 19-24 months. In female rats; a dose of 15 mg/kg may be preferred for 50 minutes of deep anesthesia in 7-12 and 13-18 month old female rats. 10 mg/kg dose may be preferred for short-term procedures in 0-6 month old female rats. However, a dose of 15 mg/kg can only be used for procedures that require superficial anesthesia in female rats over 18 months.

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Conflict of Interest: *The authors declare that they have no conflict of interest.*

Ethical Statement: *The experiments were conducted following the approval by the BAIBU Animal Research Local Ethical Committee with a date of November 13, 2015 and numbered of 2015/48.*

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