HISTOPATHOLOGICAL AND BIOCHEMICAL EFFECTS OF CHRONIC PROPOFOL EXPOSURE ON DOGS

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ABSTRACT

This study was conducted in the veterinary medical college, university of Basra. The objective of this study was to know the histopathological effect of propofol as anesthetic agent on dogs organs (central nervous system, heart, liver) and effect of propofol on liver enzymes, Propofol administration for 90 days by intravenous (into cephalic vein) into 8 adult dogs which divided into two equal groups. The control group was injected with 0.9% normal saline (1ml/kg), while the propofol group was injected with (10mg /kg) body weight of dog per day. The measured parameters AST, ALT showed a significant difference in groups between zero time and after 90 days. Also the histopathological result of brain, heart and liver showed significant changes as atrophic neurons, nerve fibers vacuolation and gliosis and histopathological result of heart section showed white areas of degenerate myocardial muscle cells with presence of adipose tissue and congested blood vessels, white areas of degenerate myocyte as infiltration of adipose tissue at pericardial region (periphery) and areas of destruction of myocardial muscle cells while the histopathological changes of hepatocyte showed septal fibrosis, bile duct proliferation, fine defuse vacuolation of hepatocyte and hypertrophic of bile duct. The uses of propofol for the long term may cause serious Histopathological injuries in many organs particularly the brain and liver that may due to its direct interaction in these structural units.

INTRODUCTION

Propofol, 2,6-diisopropylphenol, is an ultra-short acting anesthetic agent used intravenously in humans(1) and animals(2). It is a non-narcotic and non-barbiturate anesthetic agent which is usually administered for maintenance of anesthesia with rapid induction and recovery phases(3).

Propofol has been shown to be increasingly used in veterinary practice2, especially in dogs and cats(4). This is in part due to its low incidence of anesthesia-related side effects and the short half-life of the drug(5, 6) .

The clinically optimal concentration of propofol in serum is 2–5 μg/mL for operation (7). Recent studies have shown that exposure to propofol contributes to increase mortality in a rat model (8) as well as increase mortality and pathology(9).

However, an overdose of propofol may abnormally and pathologically cause propofol infusion syndrome (PRIS) accompanied by severe complications in patients (10).

The Aims of Study is toxicopathology study of long term administration of propofol (high dose) in the Brain, Heart and Liver of dogs and detection of propofol effect on some biochemical parameters including (ALT & AST) in dogs.

MATERIALS AND METHODS

Eight adult dogs (4 males and 4 females) were used for the study. The dogs were assigned to two groups of four animals per group (two males and two females. The dogs aged between 6 months and 3 years old and weighed between 15 and 25 kg. They were obtained from the local markets in Basra city and housed two dog per cage. They were fed cereal based food with meat and chicken every day. The dogs were allowed two weeks to acclimatize to local conditions.

Dogs were fasted for 12 hours but access to water was allowed *ad libitum*,(dogs cannot vomit). Animals were quietly and gently handled, Pre-anesthetic medication comprised 2 mg/kg ketamine (Fresenius Kabi, Germany) and 1.1mg/kg xylazine (VMD, Belgium), combined in the same syringe and injected into the femoral biceps muscles. After approximately 10 minutes a cannula was placed into a cephalic vein.

The dose of propofol (10mg/kg) body weight of dog in the experiment by using four dogs as propofol group and repeated daily for 90 days(11) . Blood was collected from the cephalic vein at zero time and after 90 days for biochemical liver enzymes.

RESULTS

Biochemical results

The results of biochemical study of the effect of propofol on serum AST & ALT level showed a significant ($P<0.05$) increase of serum AST and ALT level in propofol group when compared with Control group (Table 1).

Table 1: Showed the effect of propofol on serum AST enzymes level. N = 12 (Mean ± SD).

AST / Groups	ZERO time	90 Day time
Control group	13.75 ± 0.4 b	14.25 ± 0.2 b
Propofol group	13.12 ± 1.08 b	393 ± 78.7 a

*Different small letter vertically refers to presence a significant differences

Table 2: Showed the effect of propofol on serum ALT enzymes level. N = 12 (Mean ± SD).

ALT / Groups	ZERO time	90 Day time
Control group	80.25 ± 6.2 b	78.97 ± 6.85 b
Propofol group	79.12 ± 1.08 b	179 ± 41.25 a

*Different small letter vertically refers to presence a significant differences

Histopathological Results

Histopathological results of brain of propofol group showed atrophic neurons (Figure 1), : perneuronal vacuolation and gliosis (proliferation of glial cells) as in (Figure 2).

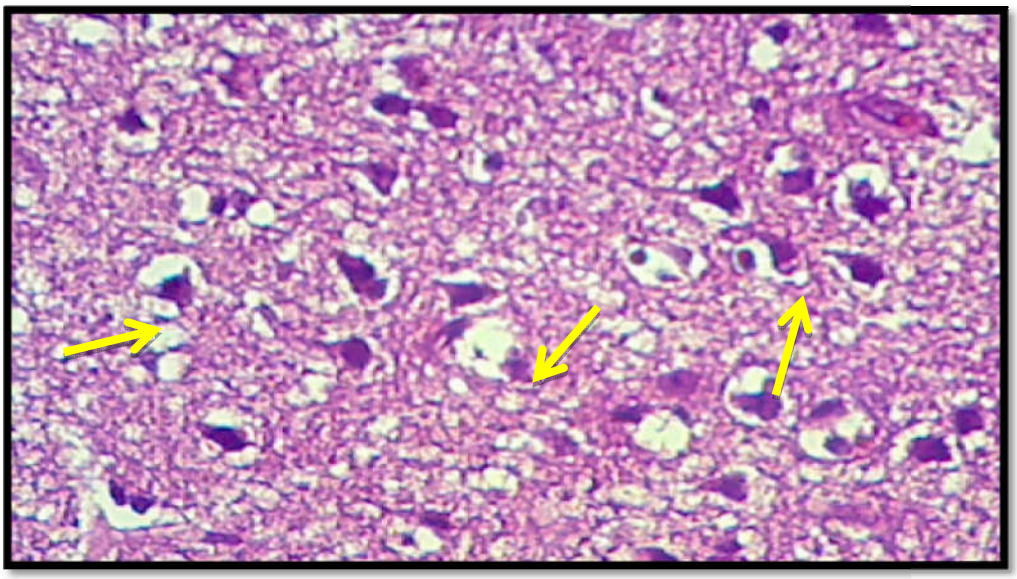

Figure 1: Histopathological section of brain of propofol group showed atrophic neurons (yellow arrow). H&E stain X400.

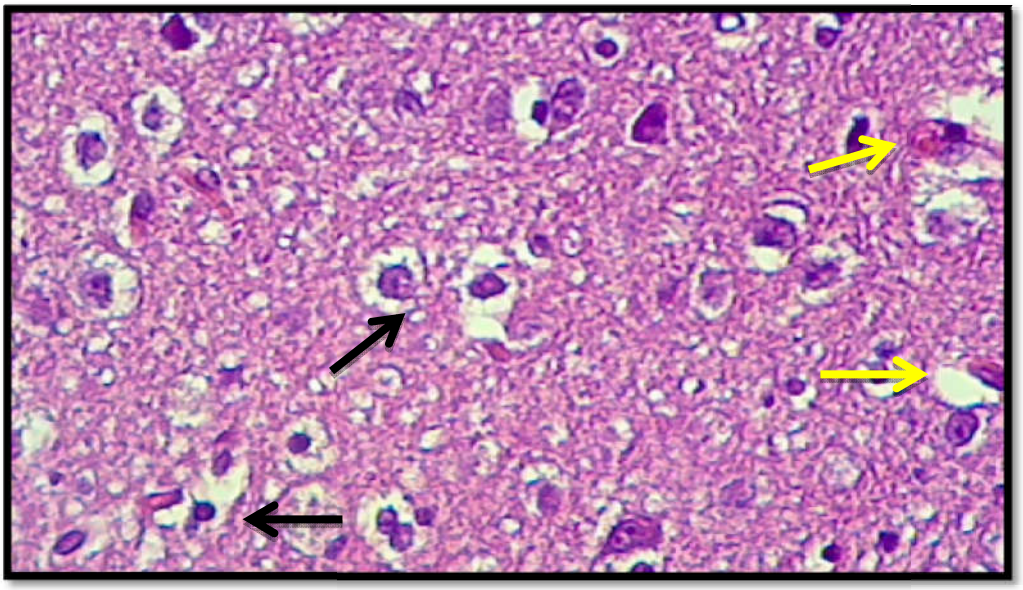

Figure 2: Histopathological section of brain of propofol group showed gliosis (proliferation of glial cells) (yellow arrow) and perneuronal vacuolation (black arrow). H&E stain X400**.**

Histopathological results of heart of propofol group showed fatty infiltration and congested blood vessels (Figure 3) and infiltration of adipose tissue at pericardial

region (periphery) (Figure 4) and areas of focal necrosis of the myocardial muscle cells (Figure 5).

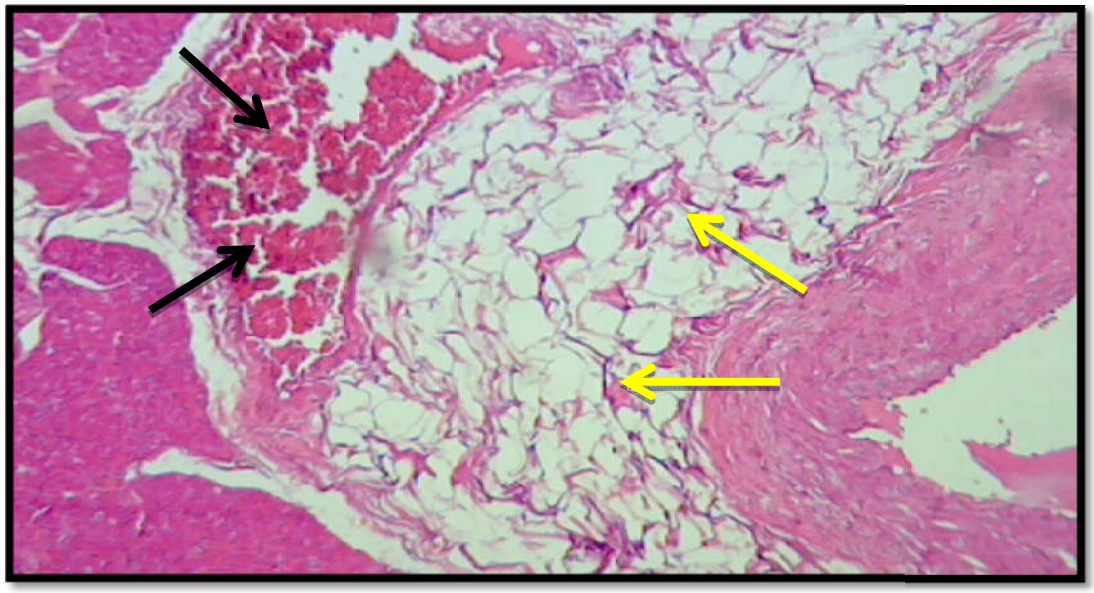

Figure 3: Histopathological section of Heart muscle of propofol group showed Fatty infiltration (yellow arrow), and congested blood vessels (black arrow) . H&E stain X100.

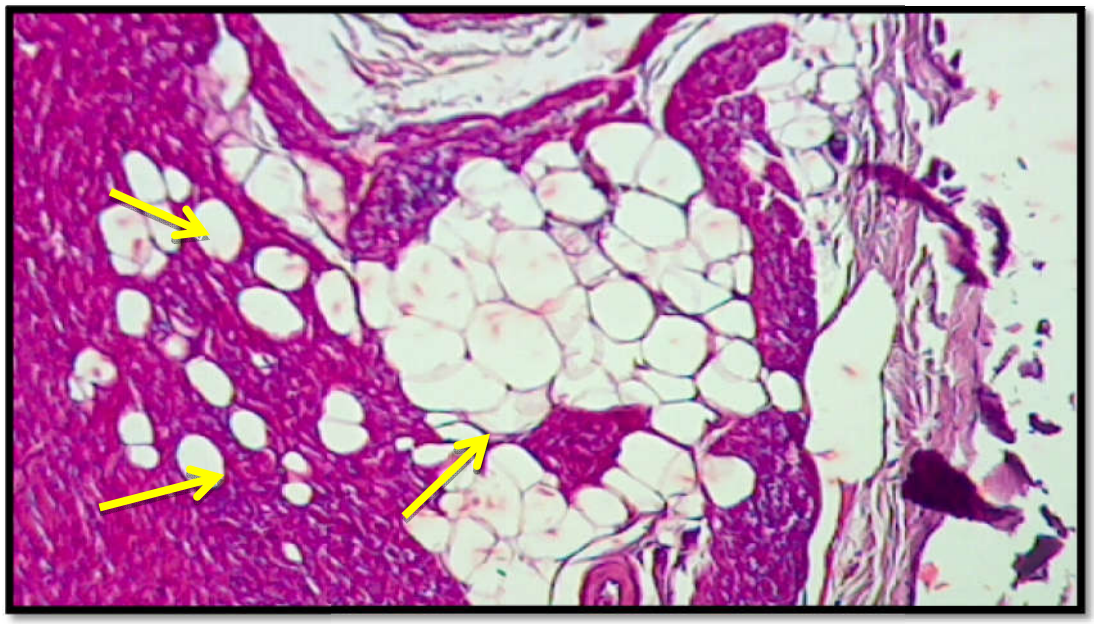

Figure 4: Histopathological section of Heart muscle of propofol group showed infiltration of adipose tissue at pericardial region (periphery) (yellow arrow). H&E stain X400.

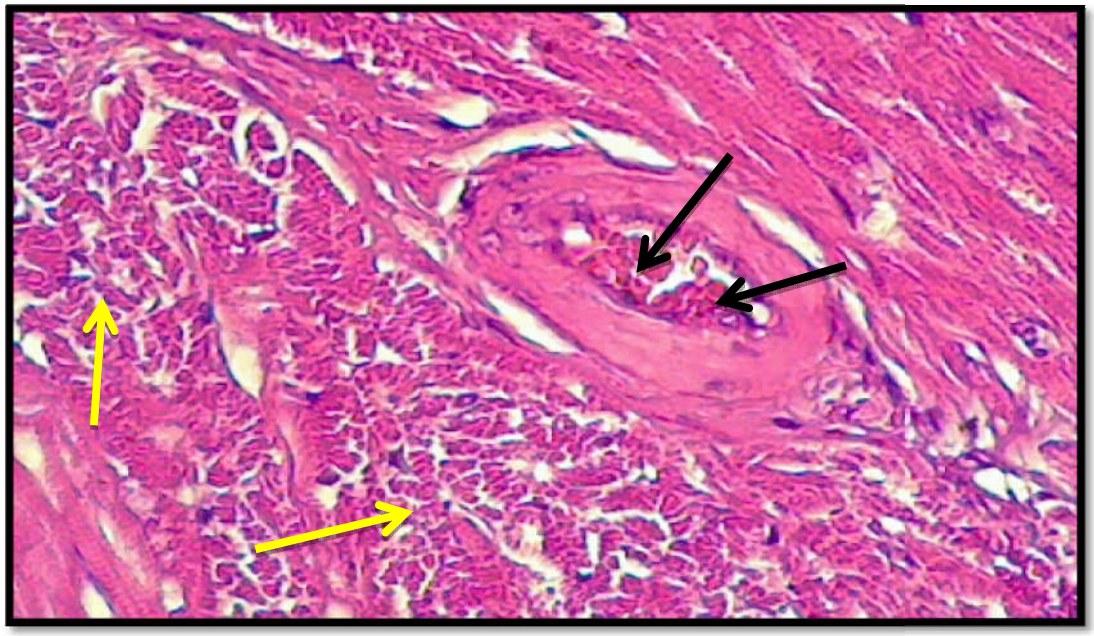

Figure 5: Histopathological section of Heart muscle of propofol group showed areas of focal necrosis of the myocardial muscle cells (yellow arrow), and congested blood vessels (black arrow). H&E stain X400.

Histopathological results of liver of propofol group showed septal fibrosis and bile duct proliferation (Figure 6), fine diffused vacuolation of hepatocyte (Figure 7) and hypertrophic of bile duct as in (Figure 8)

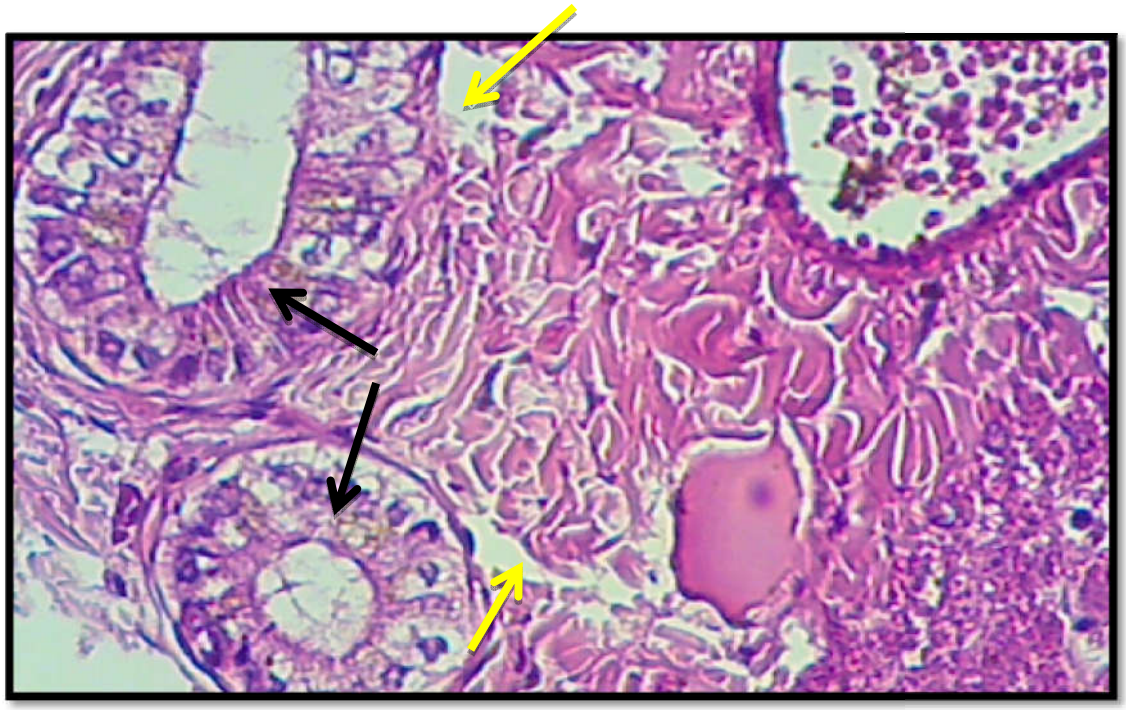

Figure 6: Histopathological section of Liver of propofol group showed area of septal fibrosis (yellow arrow), and bile duct proliferation (black arrow). H&E stain X400.

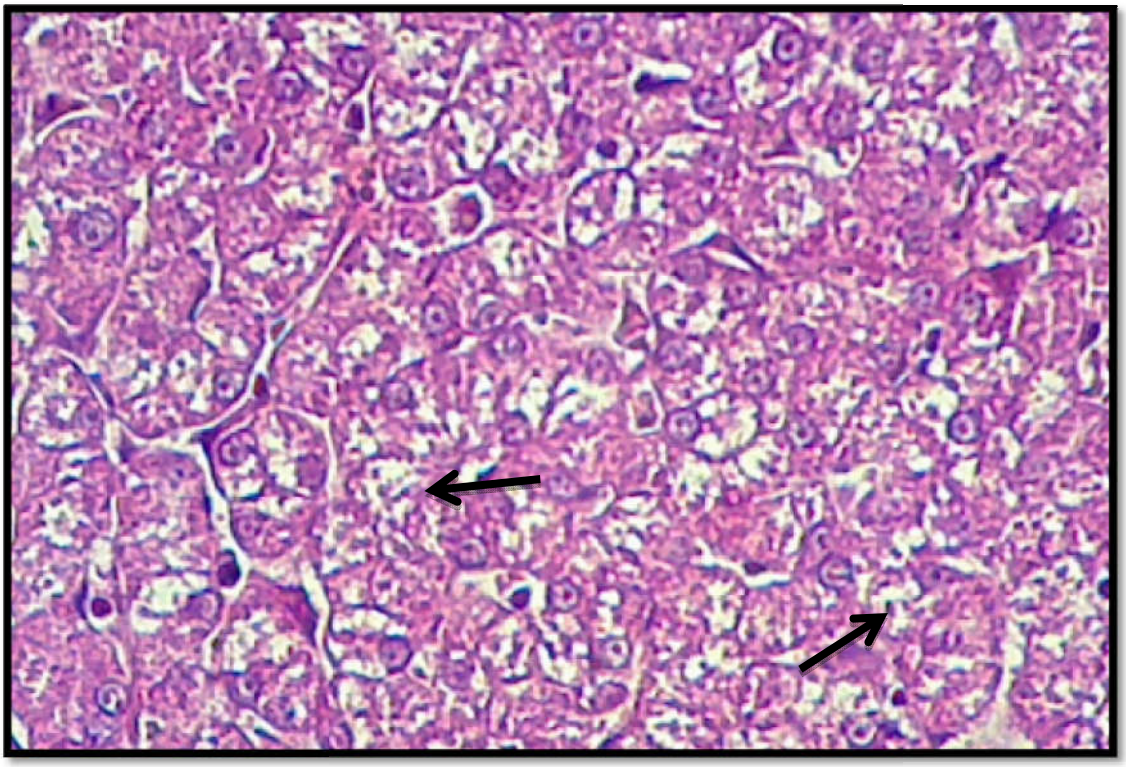

Figure 7: Histopathological section of Liver of propofol group showed fine difuse vacuolation of hepatocyte (black arrow). H&E stain X400.

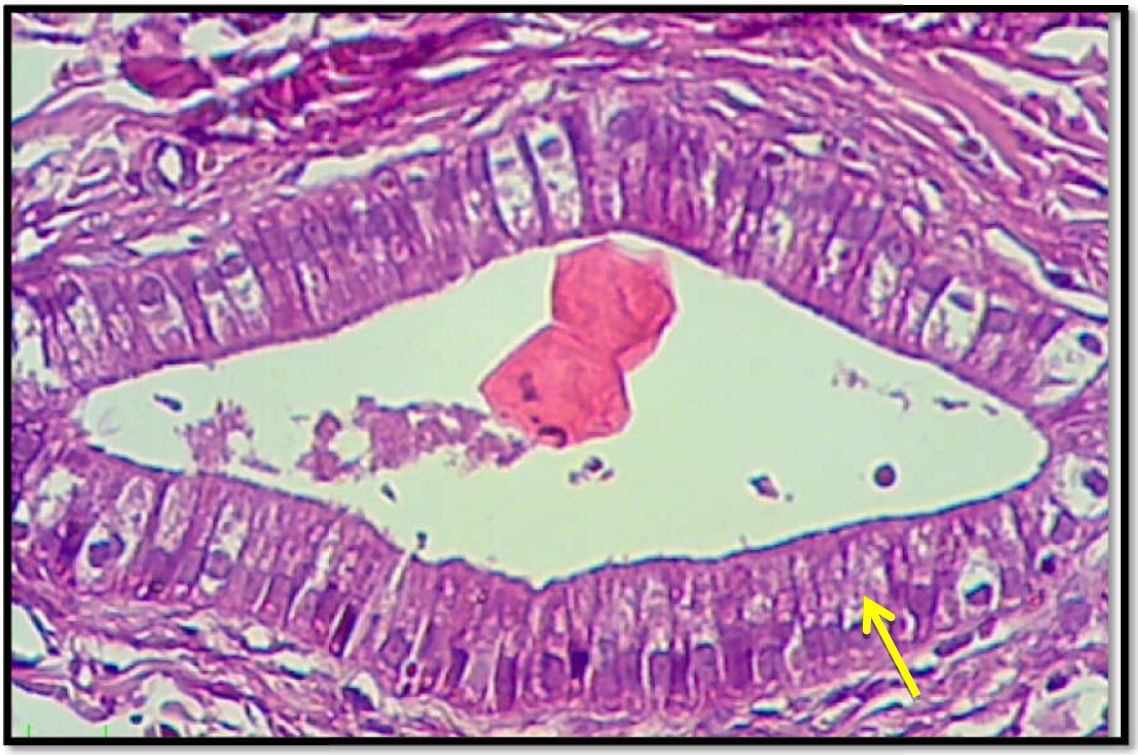

Figure 8: Histopathological section of Liver of propofol group showed area of hypertrophic of bile duct (yellow arrow). H&E stain 400X.

DISCUSSION

Effect of propofol on serum AST and ALT enzyme level

The current study showed a significant increase of serum AST and ALT levels in propofol group when compared with control group. This may be due to the propofol effect on the hepatocyte that was seen clear in histopathological section of hepatocyte (septal fibrosis, bile duct proliferation and vacuolation of hepatocyte), This result is corresponding with (Nguyen) who reported that propofol caused postoperative elevation of serum AST and ALT level in patients(12).

Our results are also in agreement with (Kneiseler) who reported that an elevated serum ALT level of pateint with developed jaundice and signs of hepatic failure one week after surgery and propofol anesthesia(13), this result may be related to irreversible injury of hepatocyte causes release of ALT into the circulation and their elevation.

From the results, it is noted that by increasing the dose of propofol the serum level of hepatic AST is significantly increased when compared with the Control group, this result may be related to the degree of hepatocytes damage caused by repeated dose of propofol. The current result is in line with (Abdelhakiem) who observed that serum AST is released from hepatocyte in proportion to the degree of tissue injury and disruption of hepatocyte(14).

Histopathological effect of propofol on Brain

From the present results neuronal cells appeared to be severely affected by high dose of propofol in which the treated groups showed atrophic neurons associated with perneuronal vacuolation. This result may be related to the toxic effect of high dose of propofol on neurons. The current result is in line with (Wei) who observed that propofol when administered at clinical concentrations for prolonged time can activate toxic mechanisms on neurons(15).

Our result of the treated group showed nerve fibers vacuolation, This result may be related to the toxic effect of high dose of propofol, The current result is in line with (Chen) who reported that effect of propofol that could promote Ca2+ dependent neuronal death is inhibition of respiration therefore any impairment of mitochondrial respiration by propofol could promote Ca2+-induced neurotoxicity(16).

On the other hand, the current study showed gliosis (proliferation of glial cells) of propofol treated group, our result is in line with (Weight) who found that lipid emulsion used as a carrier for propofol may be responsible for glial activation(17). These findings support the histopathological changes of glial cell in our results associated with propofol treatment.

Histopathological effect of propofol on Heart

The present study showed histopathological damage related to propofol administered. There were blood vessels congestion and fatty infiltration. This may be related to the damage of myocardial muscle cells in propofol group, this result is in agreement with (Wolf) who suggested that propofol toxicity might be attributed to impaired fatty acid oxidation increasing the level of malonylcarnitine and C5-acylcarnitine(18).

Our results are in line with (Kam; Krajčová) who reported that prolonged propofol overdose lead to propofol infusion syndrome (PRIS) is a rare but lethal condition characterized by cardiac failure, refractory arrhythmia, hyperlipidemia(19,20).

Our result of treated groups showed focal necrosis of the myocardial muscle cells and congested blood vessels, that may be related to high dose propofol toxicity, This result agreed with (Kam) who documented cardiovascular abnormalities with PRIS include supraventricular arrhythmias, ventricular arrhythmias, bradycardia, hypotension, and asystole (19). Causes of cardiovascular abnormalities may be a direct result of myocytolysis, hypoperfusion, cytopathic hypoxia, or alterations in beta-adrenergic receptors and calcium channel proteins.

Histopathological effect of propofol on Liver

The histopathological changes in liver tissue of propofol group showed septal fibrosis and fine difuse vacuolation of hepatocyte and bile duct proliferation and hypertrophic of bile duct. These changes related to toxic effect of propofol on hepatocyte as a result of exhaustion the capacity of centrilobular hepatocytes to metabolize high dose of propofol, this result is in consistent with (Nguyen) who found

that patient treated with propofol leads to damage of hepatocytes that related to the toxic potential of propofol to liver cells at high dose and showed acute hepatocellular injury with mild fibrosis(12).

Our result of treated group may be related to metabolism impaired by hepatocytes because of their damage by propofol, these changes occur as an adaptation of hepatocytes to compete for metabolism of propofol. This result is matched with (13,21,22) they found prolong treated with propofol lead to imbalance of the mitochondrial respiratory chain, leading to disruption on cellular energy production and, consequently, compromising Krebs cycle, metabolism of amino acids and fatty acid oxidation and consecutive cell death.

الآثار النسيجية المرضية والكيموحيوية للتعرض المزمن للبروبوفول على الكلاب

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الخلاصة

أجريت هذه الدراسة في كلية الطب البيطري بجامعة البصرة. كان الهدف من هذه الدراسة هو معرفة التأثير النسيجي للبروبوفول كعامل مخدر على أعضاء الكلاب (الجهاز العصبي المركزي والقلب والكبد) وتأثير البروبوفول على إنزيمات الكبد ، وقد تم عطاء البروبوفول لمدة ٩٠ يومًا عن طريق الوريد (الوريد الرأسي) إلى ٨ من الكلاب البالغة التي تنقسم إلى مجموعتين متساويتين. تم حقن المجموعة الضابطة بمحلول ملحي طبيعي بنسبة ٠.٩٪ (١ مل / كجم) ، في حين تم حقن مجموعة البروبوفول بجرعة (١٠ مجم / كجم) للكلب يوميًا. أظهرت الانزيمات المقاسة AST ، ALT اختلافًا كبيرًا في المجموعات بين وقت الصفر وبعد ٩٠ يومًا. كما أظهرت النتيجة النسيجية للدماغ والقلب والكبد تغيرات كبيرة مثل الخلايا العصبية الضامرة، وأعراض إفراغ الألياف العصبية والزلز والنتيجة المرضية لنسيج القلب ، أظهرت مناطق بيضاء من خلايا عضلة القلب المتدهورة مع وجود الأنسجة الدهنية والأوعية الدموية المحتقنة ، والمناطق البيضاء المتدهورة لعضلة القلب كتسلل للأنسجة الدهنية في منطقة التامور (المحيط) في حين أظهرت التغيرات النسيجية للخلايا الكبدية تليف الحاجز ، وانتشار القناة الصفراوية ، ونزع فتيل الخلايا الكبدية وتضخم القناة الصفراوية. قد تتسبب استخدامات البروبوفول على المدى الطويل في حدوث إصابات نسيجية خطيرة في العديد من الأعضاء وخاصة الدماغ والكبد التي قد تكون بسبب تفاعلها المباشر في هذه الوحدات الهيكلية.

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