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Research Article

EFFECTS OF ISOFLURANE ANESTHESIA IN UNILATERAL NEPHRECTOMIZED DOG: HISTOPATHOLOGICAL AND BIOCHEMICAL FINDINGS

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ABSTRACT
Most of inhalation anesthetics are from the halogenated group, which are widely used in general anesthesia in humans and animals. The negative effects of these drugs are included heart damage, brain injury, and liver and kidney damages in the patients. Blood Urea Nitrogen (BUN) and creatinine have been approved as the reliable indicators to evaluate renal function. The present study was performed on dogs as the most similar animal model to humans. The studied dogs underwent general anesthesia by isoflurane through inhalation method and then, they were evaluated for renal function by removing one of their kidneys at the defined time. Blood urea nitrogen, creatinine and fluoride ions were three considered indicators in the study of renal function. Also, pathology tests were conducted on some kidneys' sections. Results showed a significant increase in blood urea nitrogen and creatinine following the anesthesia with isoflurane in dogs that had nephrectomy surgery which was associated with the significant increase in blood levels of fluoride. Histopathologic examination of the studied renal tissues showed some injuries including necrosis, degeneration, atrophy and hemorrhage. Considering the obvious renal injuries which were confirmed by measuring pathological and biochemical parameters in this study, it is recommended that the inhalation anesthetic of isoflurane must not be used in patients with renal failure.

Keywords: *Isoflurane Anesthesia*

INTRODUCTION
The inhalation anesthetics are widely used in general anesthesia in humans and animals. Although the majority of these drugs are excreted from the body through lungs, but somewhat is metabolized by the liver. In prolonged anesthesia, the metabolism of the mentioned drugs has a small role in drug excretion from the body. Close to 2% of isoflurane is metabolized through oxidation and reduction ways within the anesthesia in humans and is excreted through the excretory organs. Inorganic fluoride ion is the common metabolite of halogenated inhalation anesthetics.
Isoflurane is one of halogenated anesthetics which are non-flammable, transparent, volatile and colorless liquid that creates general anesthesia by affecting on the central nervous system (Ruhalamin *et al.*, 1992; Shahbazi and Maleknia, 1988; Cousins *et al.*, 1976; Hitt *et al.*, 1975). Solubility of isoflurane in the blood and body tissues is lower than halothane and enflurane (Ruhalamin *et al.*, 1992; Hellebreker, 1986). So its particle concentration in the alveoli and arterial blood rises to 50% and 60% in the first 4-8 and 15 minutes respectively, which is faster than halothane and enflurane (Ruhalamin *et al.*, 1992; Hall and Clark, 1991; Hellebreker, 1986; Hunter and Jones, 1981). Isoflurane causes hypotension further by reducing vascular resistance while halothane does it further by direct weakening of myocardium (Ruhalamin *et al.*, 1992; Shahbazi and Maleknia, 1988). Muscle relaxant property of isoflurane is more than halothane, but its analgesia effect is less (Ruhalamin *et al.*, 1992). Use of isoflurane is more appropriate than other halogenated anesthetic agents in patients with patients with heart failure, because of its low effect on the heart (Ruhalamin *et al.*, 1992).

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The metabolism extent of inhalation anesthetics depends on several factors such as liver enzymes activities, genetic and sexual parameters (Bentley *et al.,* 1982). The pathologic effects of halothane on the liver, kidney and brain of fetus have been studied by electron microscope (Booth and Mcdonald). Blood Urea Nitrogen (BUN) and creatinine as the gold standards are used to evaluate the effects of renal failure due to increase in fluoride ion following the anesthesia with halothane and methoxyflurane (Elliott and Strunin, 1993). Wickstroem and Stefansson (1981) showed a significant difference is created between blood urea nitrogen and creatinine following repeated anesthesia with halothane that causes decrease in glomerular filtration and then renal failure (Louis, 1977). Following the repeated anesthesia with isoflurane, severe liver damages were observed that have even led to death (Chang, 1977). The patients, who have been anesthetized with isoflurane during the surgery of central nervous system, have shown increase in liver enzymes activities that the increase is much more than sevoflurane (Jaimoviech and Kecskes, 1991). Anesthesia with isoflurane in dog causes hypotension (Ettinger and Feldman, 2000). Anesthesia with isoflurane in the patients with mild renal failure causes a non-significant change in blood urea nitrogen and creatinine (Creasser and Stoelting, 1973). Since some amounts of anesthetic drugs are metabolized and excreted through the kidneys, therefore evaluating renal function during anesthesia is very important. This is even more important when the patient is suffering from renal failure. Thus in the present study, the effect of isoflurane drug on renal function is studied. For this purpose, the dogs which have been under unilateral nephrectomy are tested and the results can be used in renal failure studies of humans because of more similarity of this animal model to the humans.

MATERIALS AND METHODS

6 male dogs weighing 23.18±4.7 kg and an average age of 2 years were provided and examined their health clinically based on heart rate, respiratory rate, body temperature and CBC indicators. In order to complying animals with the new environment, they were transferred to the small animal pension two weeks before the test. During this time, Praziquantel 5 mg/kgbw and mebendazole 20 mg/kgbw and their booster within 10 days and 3 days respectively, were used orally to the animals for parasite elimination (Booth and Mcdonald).

Unilateral Nephrectomy Surgery

For nephrectomy surgery and before induction of anesthesia, the studied dogs were avoided from food for 18 hours. Before anesthesia, the cephalic vein was catheterized for fluid administration and blood sampling. Before anesthesia and surgery, venous blood samples were taken in order to measure the blood urea nitrogen, creatinine and serum fluorine. Anesthesia was performed by inhalation anesthetics on the studied dogs and after intubation, in continues anesthesia maintained by an inhalation device equipped with isoflurane vaporizer on the medium level and the left kidney was removed through the approach of animal's left flank. Blood sampling were performed again after two weeks to measure the mentioned parameters as well as the blood samples which were taken from three healthy dogs as the controls and the mentioned blood parameters were measured. Also, to ensure about the health of right kidney after nephrectomy, serum creatinine was measured.

First Phase of the Experiment

The first phase of the experiment was performed two weeks after the unilateral nephrectomy as follows:
The animals were under anesthesia with a mixture of isoflurane gas and oxygen gas for 3 hours. Before anesthesia induction, they were prohibited of eating food and no pre-anesthetic medicines were administered to the dogs. Cephalic vein was catheterized to administer fluids and take venous blood samples prior to the anesthesia. Inducing anesthesia was performed with use of anesthesia mask. Isoflurane drug was administered to the animal with the concentration of 4% and oxygen flow of 2 lit/min. following intubation, dogs was connected to anesthesia machine and the anesthesia was kept at a medium level. According to eyelash and foot reflexes, the concentrations of isoflurane and oxygen were kept at 1.5-2% and 1.5 lit/min respectively and anesthesia was continued for 3 hours.

Second Phase of the Experiment

At the second phase, doges were placed under anesthesia with isoflurane gas with the same method which was mentioned in the first phase for 6 hours.

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Venous blood samples were taken before inducing anesthesia and in 3, 6, 24, 48 and 72 hours after it to measure blood urea nitrogen and creatinine. Serum fluoride was measured using the ion potentiometric method. After taking the last blood sample, the animal was euthanized by injection of magnesium sulphate 40% and animal's right kidney was removed from the body to prepare pathological samples. Kidney samples were fixed by 10% formalin and were studied under pathology investigation.

The Studied Indicators

Three serum indicators of blood urea nitrogen, creatinine and inorganic fluoride ion were studied in order to evaluate the nephrotoxicity effect of isoflurane.

Measurement of Serum Urea

To measure the urea, Pars Azmoon kit and Berthelot method were used. In this method, the ammonia obtained from urea hydrolysis, forms a green complex through the reaction of urease enzyme with hypochlorite and sodium salicylate. The created color intensity shows the urea amount in the serum which is measured by spectrophotometer. With this method, we can measure urea concentration up to 300 mg/dl.

Measurement of Serum Creatinine

To measure the urea, Pars Azmoon kit and Jaffe method were used. In this test, creatinine and alkaline picrate form a colorful complex. The produced color intensity is proportional to the creatinine amount in the sample which is measured by spectrophotometer. The serums used for calculating the creatinine amount were taken from the animal at the similar times in the previous phase.

Measurement of Serum Fluoride

To measure the serum fluoride, potentiometric method was used as follows:

A) Determining the electrode slope: 10 ml of 1.9 ppm Fluoride Standard Solution was poured in a Baker and then 10 ml buffer of regulating ionic strength was added to it and the potential was read after 10 minutes of putting electrodes on the solution. In the second stage, .9 ppm Fluoride Standard Solution and the buffer of regulating ionic strength were also used in mentioned amounts and the electrodes were put in the solution and the potential was read after 10 minutes. Sample Analysis: 10 ml blood sample of the dog was poured into the Baker and then 10 ml buffer of regulating ionic strength was added to it and electrodes were put in the solution and the potential was read after 10 minutes. At the second stage, 0.5 ml solution containing 190 ppm fluoride was poured into the Baker and electrodes were put in the solution and the potential was registered after 10 minutes and finally serum fluoride amount was measured and calculated.

Preparation Method of Histological Samples

Samples were fixed in formalin 10% and the formalin was changed after 24 hours. The tissue samples were kept in formalin for two to three days. Then, the samples were cut into 0.5×0.5 sections and were placed in the tissue-processor devise for tissue passage. These stages were performed on the tissues: alcohol 70% for two hours, alcohol 80% for one hour, alcohol 95% for two hour, alcohol 95% for one hour, alcohol 95% for one hour, alcohol 100% for two hour, alcohol 100% for one hour, alcohol 100% for one hour, xylol for 45 minutes, xylol for 45 minutes, liquid paraffin for 2 hours, liquid paraffin for 3 hours, then embedding was performed and cut by a microtome with a thickness of 5 microns and placed on glass slide. The slides were incubated in 50-60ºC until paraffin was melted. Then, they were stained with hematoxylin-eosin (H&E): Xylol for 5 minutes, alcohol 100%, 95% and 70% each one for one minute, washing several times with distilled water, H&E color for 15-20 minutes, washing with running water for 5 minutes, acid alcohol for 20 seconds, washing with running water for 5 minutes, eosin foe 1-2 minutes, alcohol 70%, 95% and 100% each one for one minute, xylol till arbitrary time and monting at the end which means putting one drop of Canada Balsam glue on the tissue and putting a coverslip on it.

Data Analysis Method

All data are presented as mean±SD. Blood urea nitrogen, creatinine and serum fluoride concentrations were analyzed using one-way ANOVA and t-test. The statistical analysis was performed by SPSS software (version 9). $P<0.05$ was considered as the significance level.

RESULTS AND DISCUSSION

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Table 1: Comparison of BUN, serum creatinine (mg/dl) and fluoride (ppm) in the times before and after anesthesia at the first stage (Mean±SD)

Blood sampling time	Before nephrectomy	After nephrectomy	First stage of the test					
			Before Anesthesia	3h after anesthesia	6h after anesthesia	24h after anesthesia	48h after anesthesia	72h after anesthesia
Bloodbiochemical factors								
Blood Urea Nitrogen	33.157±7.420	34.333±5.425	39±2.280	45.833±2.639a	46.667±4.274	32.345±5.241	36.333±8.369	37.333±5.538
Creatinine	0.667±0.124	0.830±0.110	0.729±0.165	0.988±0.225b	0.854±0.268	0.665±0.267	0.658±0.286	0.676±0.218
Fluoride	0.122±0.0319	0.125±0.0187	0.122±0.0147	0.132±0.0358	0.128±0.0366	0.123±0.0695	0.125±0.0729	0.133±0.219

A: significant difference of BUN among before and after nephrectomy and before anesthesia (P<0.001)
B: significant difference of creatinine among before and after nephrectomy and before anesthesia (P<0.004)

Table 2: Comparison of BUN, serum creatinine (mg/dl) and fluoride (ppm) in the times before and after anesthesia at the first stage (Mean±SD) in the control group

Blood sampling time	First stage of the test					
	Before Anesthesia	3h after anesthesia	6h after anesthesia	24h after anesthesia	48h after anesthesia	72h after anesthesia
Blood biochemical factors						
Blood Urea Nitrogen	32.231±6.235	32.241±7.110	33.002±7.120	32.982±6.658	32.563±6.678	33.157±7.420
Creatinine	0.645±0.112	0.648±0.023	0.645±0.022	0.646±0.022	0.647±0.025	0.657±0.121
Fluoride	0.123±0.12	0.125±0.32	0.126±0.3	0.124±0.042	0.123±0.45	0.123±0.0329

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Table 3: Comparison of BUN, serum creatinine (mg/dl) and fluoride (ppm) in the times before and after anesthesia at the second stage (Mean±SD)

Blood sampling time	Before nephrectomy	After nephrectomy	Second stage of the test					
Blood biochemical factors			Before Anesthesia	3h after anesthesia	6h after anesthesia	24h after anesthesia	48h after anesthesia	72h after anesthesia
Blood Urea Nitrogen	33.157±7.420	34.333±5.425	40±2.280	45.867±2.639a	47.656±4.274a	48.355±5.241a	41.322±8.369	42.363±5.538
Creatinine	0.667±0.124	0.830±0.110	0.789±0.165	0.988±0.225b	0.854±0.268b	0.865±0.345b	0.758±0.286	0.706±0.223
Fluoride	0.122±0.0319	0.125±0.0187	0.146±0.0156	0.197±0.0358c	0.0268±0.0356c	0.186±0.0795c	0.127±0.0629	0.183±0.22

A: significant difference of BUN among before and after nephrectomy and before anesthesia (P<0.001)
B: significant difference of BUN among before and after nephrectomy and before anesthesia (P<0.004)
C: significant difference of serum fluoride among before and after nephrectomy and before anesthesia (P<0.003)

Table 4: Comparison of BUN, serum creatinine (mg/dl) and fluoride (ppm) in the times before and after anesthesia at the second stage (Mean±SD) in the control group

Blood sampling time	Second stage of the test					
Blood biochemical factors	Before Anesthesia	3h after anesthesia	6h after anesthesia	24h after anesthesia	48h after anesthesia	72h after anesthesia
Blood Urea Nitrogen	34.895±6.215	35.641±6.562	34.654±7.012	35.322±7.158	35.263±7.178	35.253±7.321
Creatinine	0.677±0.122	0.678±0.024	0.676±0.35	0.679±0.042	0.678±0.042	0.658±0.121
Fluoride	0.127±0.12	0.126±0.22	0.126±0.3	0.127±0.32	0.127±0.38	0.127±0.05

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Results

Biochemical Results

Before the first stage after unilateral nephrectomy, no significant difference was observed in the test parameters (blood urea nitrogen, creatinine and serum fluoride) with after surgery time. in the first stage of the test, the amounts of blood urea nitrogen and serum creatinine in 3 and 6 hours after anesthesia showed a significant difference with the stages before nephrectomy, after nephrectomy and before anesthesia, but a significant difference was not observed between these times and times before and after nephrectomy and before anesthesia regarding fluoride (tables 1 and 2).

At the second stage of the test, the amounts of all three factors (BUN, Creatinine and serum fluoride) showed a significant difference in 3, 6 and 24 hours after anesthesia with the times before and after nephrectomy and before anesthesia (tables 3 and 4).

Pathology Results

With the naked eye, no signs of hyperemia, necrosis or ischemia in the tissues of right and left kidneys were observed. But in microscopic examination, renal tissue changes such as urinary tubules expansion, hydropic degeneration, and vacuolization, replacement of the connective tissue, atrophy, necrosis and hemorrhage were seen (Figures 1-7).

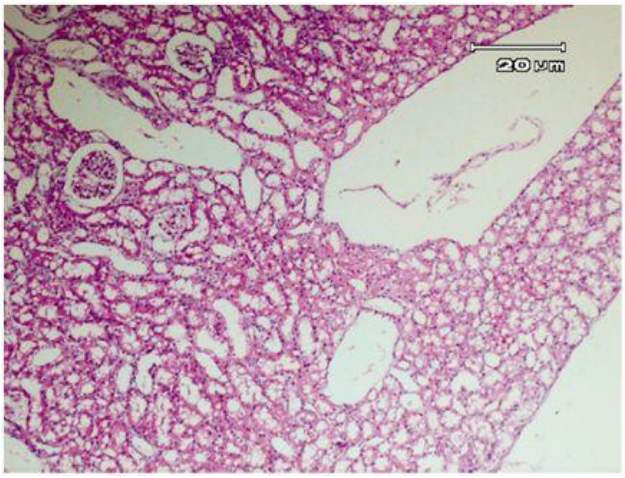

Figure 1: Urinary tubules expansion in the renal cortex associated with a reduction of the cells in glomeruli of hydropic degeneration in urinary tubules (H&E, 10 xs)

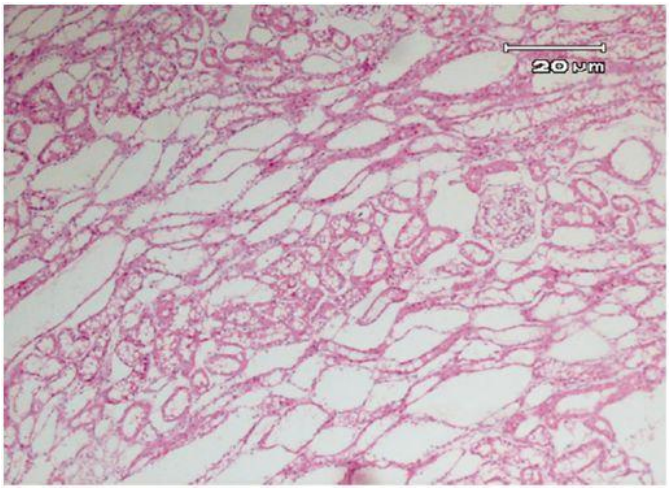

Figure 2: Reduction of the cells and vacuolization associated with urinary tubules expansion (H&E, 10 xs)

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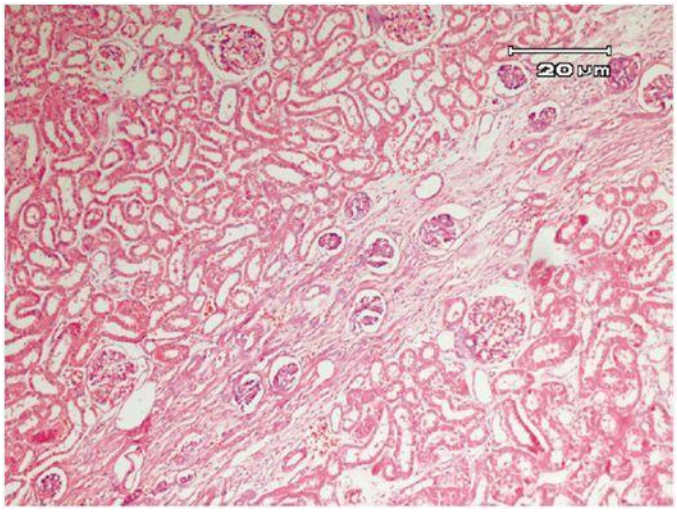

Figure 3: Focal atrophy and urinary tubules destruction and replacement of the connective tissue (H&E, 10x)

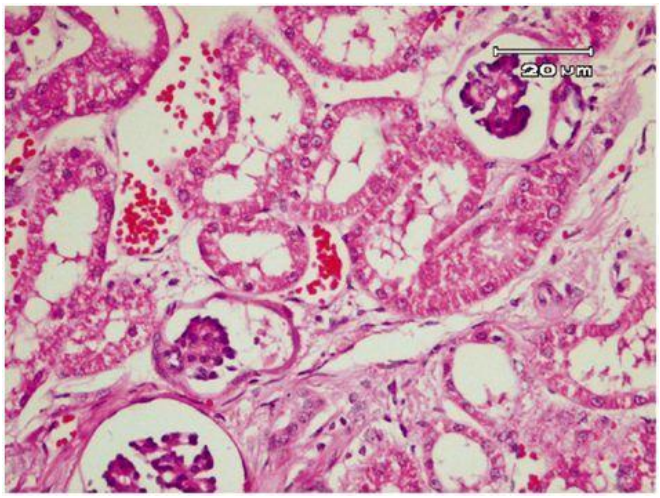

Figure 4: Focal atrophy of glomeruli associated with necrosis and hydropic degeneration in certain cells of urinary tubules walls (H&E, 40 xs)

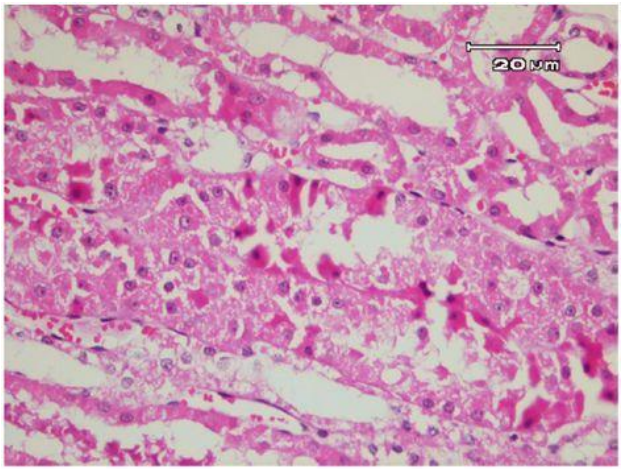

Figure 5: Necrosis of the epithelial cells associated with hydropic degeneration of cells (H&E, 40 xs)

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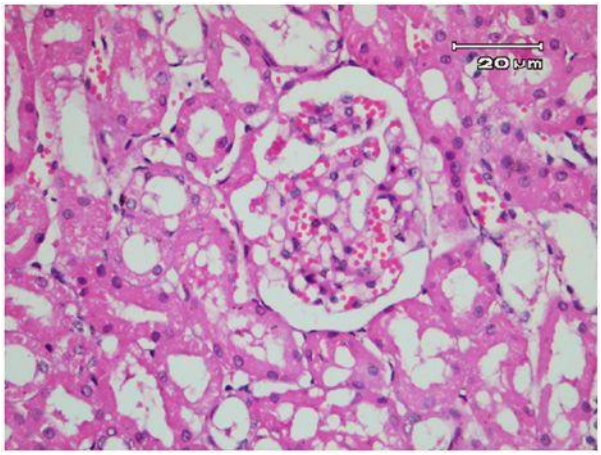

Figure 6: Atrophy and vacuolization of the glomeruli associated with degeneration and necrosis and hydropic degeneration in urinary tubules (H&E, 40 xs)

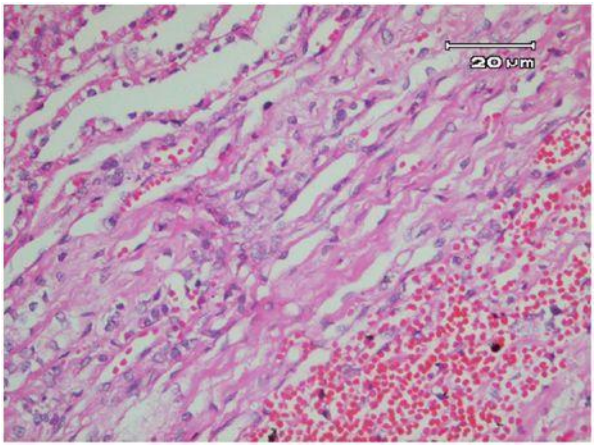

Figure 7: Hemorrhage in the kidney (H&E, 40 xs)

Discussion

In the present study, anesthesia induced by the anesthesia mask through isoflurane drug and pre-anesthetic and anesthetic drugs were used to prevent interaction with the metabolism of isoflurane. Drug interaction can include incompatibility of two drugs, disturbance in absorption of one drug by the other ones, interfere with the action of the enzyme metabolizing a drug and or disturbing of binding of a drug to the protein, changes in liver or kidney excretions of a drug, changes of drug excretion through the lungs and changes in drug distribution in body tissues and finally change in the drug metabolism (Thurmon *et al.*, 1996).

Many drugs are metabolized by redox system in the liver and in the next step, their excretion in the urine or bile is accelerated with the conjugation. Changes in metabolizing enzymes is clinically very important in anesthesia that these changes in drugs' effects can be included the inhibitory or stimulatory effects on the liver enzymes. For example, using barbiturates before the anesthesia with halothane can cause an increase in the production of organic fluoride toxic metabolites due to the halothane that this toxic metabolite can have toxic effects on the liver and kidneys (Thurmon *et al.*, 1996). It has been found that the nephrotoxicity resulted from methoxyflurane administration is directly related to the metabolism of anesthetic drug and production of inorganic fluoride ion. Enzymatic induction can increase the metabolic rate and thus increase in production of in-organic fluoride ion. In the laboratory studies on a group of rats, it was found that enzymatic induction by Phenobarbital or phenytoin causes an increase in de-fluorinating of methoxyflurane but has no effect on enflurane and isoflurane. In the lab, de-fluorination of

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methoxyflurane showed more increase compared to the other anesthetics. This studies show that treatment with enzyme inducing drugs increases the nephrotoxicity risk if the used anesthetic drug is methoxyflurane (Hitt and Mazz, 1977). Increased serum fluoride concentration during anesthesia with halothane and sevoflurane and enflurane has been reported in human and rat (Cousins *et al.*, 1976; Wickstrom and Stefansson, 1981; Young *et al.*, 1975). A methoxyflurane toxic effect on the kidneys is decrease in glomerular infiltration rate with an increase in blood urea nitrogen and creatinine. By increasing the amount of fluoride to 50 to 80 µmol/lit (0.95-1.52 ppm), these effects begin and when they reach to 80-175 µmol/lit (1.52 – 3.325 ppm), renal toxicity is quite evident (Cousins *et al.*, 1976). In the present study, the ultimate limit of fluoride in the second stage of anesthesia was 0.128 ppm which was not able to produce renal toxicity. Based on the clinical experiences with methoxyflurane, it was found that the doses higher than 50 µmol/lit of inorganic fluoride ion is nephrotoxic. No cases of renal failure due to prolonged anesthesia with enflurane have not been reported (the metabolic rate of this drug is 2.4%). Also, sevoflurane has not produced any toxicity depended to fluoride ion in the animals during the clinical studies and in the patients with the history of renal failure. Nephrotoxicity threshold of fluoride ion is 50 µmol/lit and may not be true for enflurane and sevoflurane. Therefore, the increased fluoride concentration which is recorded following the anesthesia with sevoflurane has no clinical significance (Nuscheler *et al.*, 1996). According to table 2-2 and due to the probable low metabolism of sevoflurane (3%), the amount of released fluoride does not have nephrotoxic effects. Half-life of inorganic fluoride is 90 minutes in the blood, but the peak level of inorganic fluoride remains high for three days after methoxyflurane administration, but reduces rapidly after anesthesia with enflurane because methoxyflurane is fat-soluble 10 times higher than enflurane. Therefore, methoxyflurane remains in the body till days after the last administration and is accessible to metabolize to inorganic fluoride after anesthesia (Mazze, 1984). The patients who were anesthetized with halothane for a long time showed an increase in the maximum urinary osmolality in one day after anesthesia. The maximum amount of serum fluoride was 33.6 µmol/lit and remained above 20 µmol/lit for 18 hours. It was found that the nephrotoxicity threshold of fluoride ion is less than the mentioned 50 µmol/lit, before (Mazze *et al.*, 1997). Ivan *et al.*, indicated that renal failure is caused by the increased concentration of fluoride ion in the anesthesia with halothane and methoxyflurane and introduced the measurements of blood urea nitrogen and creatinine as the gold standard to evaluate the kidneys (Kharasch *et al.*, 2001). In the present study, a significant increase in blood urea nitrogen and also serum creatinine after anesthesia compared to the times before and after nephrectomy and before anesthesia can be due to the nephrotoxic effects of fluoride ion in the long term in dogs with nephrectomy surgery and on healthy kidney. In the studies by Lewis *et al.*, (1977), renal changes following the anesthesia with halothane were shown by electron microscope. Adult mice which were anesthetized for 4 to 8 weeks with a dose of 10 to 500 ppm halothane, showed the renal injuries as lysosomal aggregation in the cytoplasm of epithelial cells of proximal tubules and also accumulation of spherical structures in basal membrane of these cells and accumulation in smooth endoplasmic reticulum. Also, the pathologic changes in the kidneys of all mouse newborns which were exposed to 10 ppm halothane before the birth have been reported as general degenerative changes and lysosomal aggregation and lipid droplets (Louis, 1977). The toxic effects of isoflurane on the liver and brain have been studied. The progressive signs have shown that liver degeneration can be induced after exposure to isoflurane (Nuscheler *et al.*, 1996). Also in the present study, pathologic effects of isoflurane on the renal tissue were observed as inflammation of nephrons and also hemorrhage in the renal cortex which can be indicated that in prolonged anesthesia with isoflurane in dogs with renal failure, signs however mild are observed that these pathological signs are minimum compared to halothane and methoxyflurane. Using isoflurane causes decrease in renal blood flow and renal filtration rate (Wickstorm, 1976). The decline in long term can explain the slow renal destruction in these patients. All halogenated inhalation anesthetics are able to develop liver and kidney toxicity in various animal species and humans (Burtis and Ashwood, 1994; O'Brien *et al.*, 1986; Ray and Drummond, 1989). The studies have shown that reduced oxygen before activation of liver enzymes or prolonged decrease in arterial blood pressure increase the risk of liver and kidney injuries after anesthesia

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(Maiorino *et al.*, 1981; McLain *et al.*, 1979; Young *et al.*, 1975). Based on blood gas analysis during anesthesia, oxygen and carbon dioxide were kept in the normal range in all dogs. Therefore, dogs have not experienced hypoxia or accumulation of carbon dioxide gas in no times within anesthesia. As mentioned, hypoxia can affect on metabolism of halothane and isoflurane (Bentley *et al.*, 1982; Maiorino *et al.*, 1981; McLain *et al.*, 1979; Young *et al.*, 1975).

To ensure about the health of right kidney, serum creatinine was measured in the second week after nephrectomy and the result was in consistent with the normal serum creatinine in healthy dogs (0.8 – 1.8 mg/dl). Thus it can be clinically considered as a glomerular filtration. Reduced creatinine clearance is unexpected in unilateral renal diseases or kidney removal if the other kidney is healthy (Ruhalamin *et al.*, 1992).

Isoflurane fumigation time to animal can cause an increase in isoflurane metabolism and inorganic fluoride ion, reduced renal blood flow and its toxic effects on kidney. At the end and according to the low percentage of produced fluoride ion and its short half-life resulted from isoflurane metabolism in short-term anesthesia, it can be concluded that this drug can be used as a safe drug, but using isoflurane during the long-term anesthesia in patients with renal failure can lead to pathologic injuries in the kidneys.

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