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Histopathological Effects of Desflurane on the Liver and the Kidney Using Light Microscopy

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Abstract: The aim of this study was to histopathologically assess the toxic effect of desflurane on the liver and the kidney. The rats (n = 150) were grouped into five main and three subgroups according to the exposure time to the anesthetic agent. The first group was planned as 1 MAC Desflurane+N_2O+O_2, the second group as 1 MAC Desflurane+O_2, the third group as 2 MAC Desflurane+N_2O+O_2, the fourth group as 2 MAC Desflurane+O_2 and the 5th group as the control group. Each group was given the anesthetic agent for 1, 3 or 6 h. The rats that were exposed to the anesthetic agent with an adequate dose and for an adequate period of time were sacrificed properly. Livers and kidneys were resected and examined by light microscopes following the routine tissue follow-up procedures. Significant histopathological changes were observed in all groups compared to the control group. However, the pathological findings of the group 2 MAC Desflurane+N_2O+O_2 at the 6th h with the light microscope was significantly more than those of other groups at all times. It was concluded that although, desflurane caused cellular changes in liver and kidney tissue, it did not cause any clinical changes. Nevertheless, further studies are required to support this opinion.

Key words: Desflurane, light microscopy, liver, kidney, rat, Turkey

INTRODUCTION

Desflurane which has been widely used in humans for general anesthesia since 1990 is metabolized in the liver at a rate of 0.02% (Miller *et al*., 2000; Sutton *et al*., 1991). This low metabolism is considered to be responsible for the low toxicity on this organ. It has also been suggested that it is not toxic to the kidney as it does not cause fluorine release (Miller *et al*., 2000; Sutton *et al*., 1991; Njoku *et al*., 1997; Weiskopf *et al*., 1992). However, it is not known whether or not it has histopathological toxicity on the liver and the kidney. It is routinely used in various concentrations and periods for general anesthesia in humans (Weiskopf *et al*., 1992). The aim of this study was to assess the histopathological effects of desflurane on the liver and the kidney using light microscopy.

MATERIALS AND METHODS

The study was approved by the Ethics Committee. Inbred Sprague-Dawley species of rats (n = 150) were included in the study. Male Sprague Dawley rats (200-250 g) bred in the Animal House, Yuzuncu Yil University were fed on standard rat diet and water *ad libitum*. The rats were grouped into 5 main and 3 subgroups according to the exposure time (1, 3 or 6 h) to the anesthetic agent. With a semi-closed system, the 1st group was given 1 MAC Desflurane+N_2O+O_2 (n = 30), the 2nd group was given 1 MAC Desflurane+O_2 (n = 30), the 3rd group was given 2 MAC Desflurane+N_2O+O_2 (n = 30) and the fourth group was administered 2 MAC Desflurane+O_2 (n = 30) for 1, 3 and 6 h. The 5th group (n = 30) was the control group and was only given O_2. Each group received the anesthetic agent for 1, 3 or 6 h. The rats which were exposed to the anesthetic agent at an adequate dose for an adequate period of time were sacrificed properly. The livers and the kidneys were resected and examined by light microscopes following the routine tissue follow-up procedures. The 1st, 2nd, 3rd and the 4th groups rats were sacrificed by cervical dislocation using desflurane anesthesia and the control group using intraperitoneal ketamine. The vet performed the liver and kidney resections. The samples for the light microscope were placed in 10% formalin solution. The liver and the kidney samples were transferred to paraffin blocks, sections were performed, stained using hematoxylene-eosine and examined at 20-40 magnification following the routine fixation procedures.

Liver tissue was assessed with the light microscope according to the portal and sinusoidal infiltration, portal and parenchymal fibrosis, hepatocyte changes (hydropic degeneration, micro and macro vesicular lipoidosis,

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apoptosis, nuclear changes), focal necrosis, bridging necrosis, submassive and massive necrosis, portal and infrahepatic biliary stasis, biliary canalicular changes and Kuppfer cell changes. Renal tissue was assessed according to tubular and glomerular changes. The severity of cellular changes was graded as not at all, random, mild, moderate and significant. The Student's t and the Mann-Whitney-U tests were used to find if there was a significant difference between the study groups. The level of significance was set as $p<0.05$.

RESULTS AND DISCUSSION

There was a mild balloon degeneration and perivenular focal necrosis at 1 h and more significant balloon degeneration at 3 h compared to 1 h, councilman body (apoptotic body), confluent necrosis at 3 h and normal findings at 6 h in the livers of rats of the 1 MAC Desflurane+N_2O+O_2 group. There was less significant balloon degeneration compared to 1 h of the group receiving 1 MAC Desflurane+N_2O+O_2, partial confluent necrosis, mononuclear cell infiltration in the portal region; there was mild balloon degeneration and confluent necrosis at 3 h and only focal necrosis at 6 h in the group of 1 MAC Desflurane+O_2. There was scarce balloon degeneration and focal necrosis at 1 h perivenular confluent necrosis, balloon degeneration and focal necrosis at 3 h and significant balloon degeneration, focal necrosis and confluent necrosis at 6 h in the group of 2 MAC Desflurane+N_2O+O_2. There was confluent necrosis, single cell necrosis and scarce balloon degeneration at 1 h confluent necrosis, focal balloon degeneration and scarce microvesicular steatosis at 3 h and mononuclear cell infiltration at some portal areas and single cell necrosis at 6 h in the group of 2 MAC Desflurane + O_2 (Fig. 1). The liver was normal in the control groups (Fig. 2). Three animals died in this group before completing the study and were hence excluded from the study.

There was focal loss in the epithelial tubular cells at 1 h and normal findings at 3 and 6 h in the kidneys of the group with 1 MAC Desflurane+N_2O+O_2. There were normal findings at 1 h; there was tubular epithelial cell degeneration at 3 h and milder tubular epithelial cell degeneration at 6 h compared to the 3 h kidneys of the group with 1 MAC Desflurane+O_2. There was tubular epithelial cell degeneration at 1 h; tubular epithelial cell degeneration and cystic dilatation at 3 h and significant tubular epithelial cell degeneration at 6 h in the kidneys of the 2 MAC Desflurane+N_2O+O_2 group. There was tubular necrosis and fibrin deposition in the glomeruli at 1 h, normal findings at 3 h and tubular epithelial cell degeneration, tubular atrophy and tubular necrosis at 6 h in the kidneys of the 2 MAC Desflurane+O_2 group (Fig. 3). The livers were visualized as normal in the control groups (Fig. 4). Three animals died in this group before

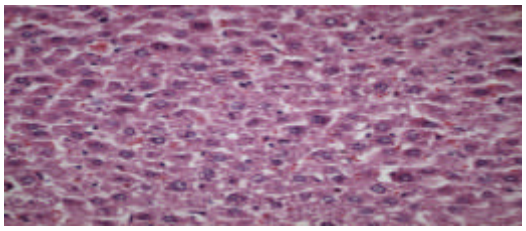

Fig. 1: Balloon degeneration and confluent necrosis. Light microscopy (20-40 amplification)

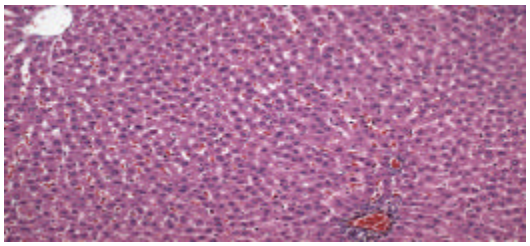

Fig. 2: Normal liver. Light microscopy (20-40 amplification)

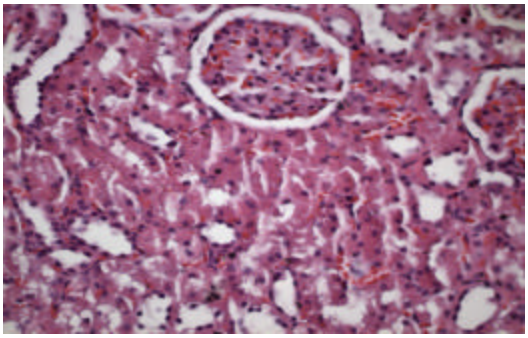

Fig. 3: Tubuler necrosis in Kidney. Light microscopy (20-40 amplification)

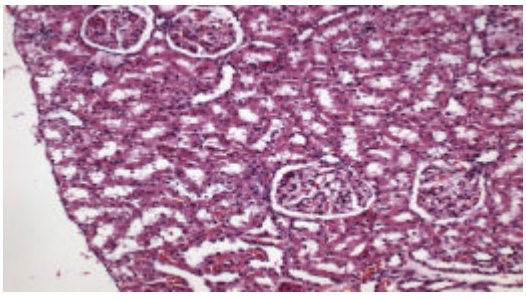

Fig. 4: Normal kidney. Light microscopy. Light microscopy (20-40 amplification)

completing the study and were hence excluded from the study. Inhalation anesthetics have brought along organ toxicity ever since they have been in use with preponderance of liver and kidney toxicities. The liver was the first organ to be considered as it is the site of metabolization of inhalation anesthetics (Miller *et al*., 2000). The spectrum of hepatotoxicity due to inhalation anesthetics changes from mild hepatic dysfunction to massive hepatic failure. The causes may be hepatocellular damage, cholestasis, changes in the bilirubin metabolism and immunological effects. It is difficult to consider hepatotoxicity to be definitely due to inhalation agents. All anesthetic techniques contribute to hepatic dysfunction by decreasing the hepatic blood flow. The hepatic blood flow is affected to a greater extent by the site of surgery than the anesthetic agent or technique. Human studies have reported that desflurane is not toxic to the liver (Miller *et al*., 2000). In another study with volunteers (Weiskopf *et al*., 1992), it was reported that long-term and high concentration desflurane use did not cause hepatic injury. However, fulminant hepatites were reported in 3 cases receiving desflurane anesthesia (Berghaus *et al*., 1999; Tung *et al*., 2005; Martin *et al*., 1995), however, it was reported that these patients underwent previous general anesthesia for various reasons. The toxicity was hypothesized to be due to hypersensitivity to halothane and trifluoroacetic acid which is the metabolite of desflurane and serum antibodies that had developed against hepatic microsomal proteins. However, there is scarce data on humans and animals to support this hypothesis (Berghaus *et al*., 1999; Tung *et al*., 2005; Martin *et al*., 1995; Ghantous *et al*., 1991). Histopathological changes in the liver tissue were found in the study with the light microscopes in all study groups. However, it was commented by a pathologist that although, these findings were significant when compared to the control group, they had no clinical significance.

Inhalation anesthetics reduce the urinary flow, GFR, renal blood flow and electrolyte excretion by depressing the renal functions. These changes are usually secondary to cardiovascular, sympathetic and endocrine systems and are usually reversible in the short-term following surgery and anesthesia (Miller *et al*., 2000). No nephrotoxicity could be demonstrated in clinical studies with desflurane. This has been attributed to the extreme resistance of desflurane to defluoration and to the non-increased concentrations during the surgical procedure. Thus, desflurane is not considered to cause renal damage (Miller *et al*., 2000; Weiskopf *et al*., 1992; El-Eger *et al*., 1997a, b). Histopathological changes in the kidney tissue were found in the study with the light microscope in all study groups. However, it was commented by a pathologist that although these findings were significant when compared to the control group, they were of no clinical significance.

CONCLUSION

In this study, although desflurane caused cellular changes in the liver and kidney tissues, this had no clinical significance. However, further studies are required to support these findings.

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