The effects of ketamine and thiopental used alone or in combination on the brain, heart, and bronchial tissues of rats

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Abstract

Introduction: We compared the side effects of ketamine and thiopental used alone and of a ketamine/thiopental combination dose on the brain, heart, and bronchial tissues of rats.

Material and methods: Three groups received intraperitoneal injections of 30 mg/kg ketamine (K-30); 15 mg/kg thiopental (T-15); or of both in combination (KTSA). These doses were doubled in another set of study groups (K-60, T-30, and KTA groups, respectively). Optimal anesthesia duration was examined in all groups.

Results: Anesthesia did not occur with 30 mg/kg ketamine or 15 mg/kg thiopental. However, when used alone ketamine and thiopental led to oxidative stress in the striatum, heart, and bronchial tissues. Conversely, combined administration of anesthetics and subanesthetic doses were found not to create oxidative stress in any of these areas. The highest level of adrenaline in blood samples collected from the tail veins was measured in the KTA-60, and the lowest amount in the T-30. Creatine kinase activity was highest in the KTA-60 group (p < 0.001). When we compared for all 5 groups to untreated control group; the creatine kinase-MB activities were significantly different in K-30, T-15 and T-30 (p < 0.001).

Conclusions: The studied doses of ketamine led to oxidative stress by increasing the amount of adrenaline. Thiopental increased oxidative stress with decreases in adrenaline. A longer anesthetic effect with minimal adverse events may be achieved by ketamine and thiopental in combination.

Key words: ketamine, thiopental, cardiotoxicity, neurotoxicity, oxidative stress.

Introduction

An ideal anesthetic agent should have a quick onset of effect with a wide confidence interval while not leading to side effects. Patients
should also rapidly recover after amnesia [1]. Inhaled agents used in the induction and maintenance of general anesthesia show onset of effects within a few minutes of administration. Intravenous anesthetics that start working in a shorter period of time have been produced. Two of these agents are ketamine and thiopental [2]. However, some side effects of intravenous anesthetic agents may limit their use.

Ketamine (for which we investigated the effects on brain and heart tissue as well as its effects on bronchial tissue) is an intravenous anesthetic agent derived from phencyclidine [3, 4]. Ketamine has been experimentally proven to increase the production of catecholamines in animals, including endogenous adrenaline, noradrenaline, and dopamine [5]. It has been reported in the literature that with use of ketamine at certain doses free radicals were increased and the ganglia were exposed to oxidative damage in the basal ganglia, which have a greater amount of catecholamines [6–8]. Specifically, in the brain tissue of a rat model with symptoms of ketamine-induced schizophrenia, the amount of malondialdehyde (MDA), an oxidant, is elevated, while the amount of thiol, an antioxidant, is reduced [9]. Ketamine has also been reported to increase arterial blood pressure and heart rate [3]. Ahiskaliloglu et al. argued that ketamine causes oxidative damage in heart tissue by increasing the production of oxidants such as MDA, creatine kinase-MB (CK-MB), and cardiac troponin-I and suppressing the production of antioxidants such as total glutathione [10]. With respect to oxidative stress, levels of enzymatic antioxidant parameters such as glutathione reductase (GSHRd) and glutathione peroxidase (GPO) decrease [11]. Nitric oxide (NO) levels are also used to evaluate tissue damage, as NO is an important bioregulatory molecule that plays an important role in physiological and pathophysiological processes [12]. The side effects of ketamine on the heart and vessels are thought to result from its sympathomimetic activity [13]. With respect to the impact on the bronchial tissues, ketamine has been reported to cause bronchodilation via the discharge of catecholamine through the central pathway [14].

The second compound for which we investigated effects on the tissues of the heart and brain as well as on bronchial tissue is thiopental [15]. Unlike ketamine, thiopental reduces the amount of endogenous adrenaline, noradrenaline, and dopamine in animals [16]. Thiopental use decreases systemic blood pressure [17], potentially leading to high-risk complications such as hypotension and cerebral vascular events [18]. Cardiac pulse power has also been found to be reduced during thiopental use [17]. Ebert et al. reported that thiopental creates bronchospasm by inhibiting sympathetic activity [19]. Collectively, this information suggests that the effect of the combined use of ketamine and thiopental on the brain, heart, and bronchial tissues may be less than that observed with each compound individually. During our literature search, we did not find any studies that included effects potentially resulting from combination therapy instead of separate use of ketamine or thiopental. Therefore, the objective of this study was to compare the side effects of ketamine and thiopental, used separately and in combination, on the brain, heart and bronchial tissues of rats.

### Material and methods

#### Experimental animals

Experimental animals were obtained from Ataturk University, Medical Experimental Research and Application Center. A total of 56 male Albino-Wistar rats (3 months of age; weight between 210 and 220 g) were randomly selected for the experiment. The animals were housed and fed in the pharmacology laboratory at normal room temperature (22°C) for 1 week prior to the experiment to adapt them to their environment. Animal experiments were performed in accordance with the National Guidelines for the Use and Care of Laboratory Animals and were approved by the local animal ethics committee of Ataturk University, Erzurum, Turkey (Ethics Committee Number: 2015/114, Dated: 29.06.2015).

#### Chemical agents

Ketamine was obtained from Pfizer (Turkey). Thiopental sodium was provided by I.E. Ulagay (Turkey).

#### Animal groups

Animals were divided into groups that received 30 mg/kg ketamine (K-30), 15 mg/kg thiopental (T-15; a sub-anesthetic dose), or 30 mg/kg ketamine + 15 mg/kg thiopental (KTSA), and an untreated control group (UCG). Additional groups were administered double these doses: 60 mg/kg ketamine (K-60), 30 mg/kg thiopental (T-30), and 60 mg/kg ketamine + 30 mg/kg thiopental (KTA).

#### Experimental procedure

In this study, the K-30, T-15, KTSA, K-60, T-30, and KTA groups (n = 8 for each group) were given intraperitoneal doses of ketamine and thiopental at the doses previously described. Distilled water was given to the UCG at the same volume as the solvent used for the other groups. Thiopental 15 mg/kg and ketamine 30 mg/kg did not induce anesthesia; the higher doses (30 mg/kg and
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60 mg/kg, respectively) did [5]. The appropriate level of anesthesia for surgery was determined by the point at which the experimental rats showed no reaction to a minor incision of the anterior part of the abdomen, but rather remained in the supine position [20]. Anesthesia was considered terminated when the animals reacted to incision via the initiation of head movements while in the supine position. Anesthesia duration was examined in all groups after drug administration [21].

At the end of this procedure, all animals were killed by decapitation, and oxidant and antioxidant parameters were analyzed in their brain, heart, and bronchial tissues. Adrenaline levels were measured in the blood samples collected from the tail vein. After decapitation, the brain was quickly removed from each rat, dissected, and frozen on dry ice powder. The frontal cortex and hippocampus were weighed and stored at −20°C. The whole heart tissue and the bronchial tissue proximal to the lung were dissected. Tissues were stored at −20°C before being sent to the biochemistry laboratory. The biochemical outcomes obtained from the groups administered ketamine, thiopental, or a combination (KTC) were then compared with the outcomes in the control group.

Malondialdehyde (MDA) analysis

Malondialdehyde measurements are based on the method used by Ohkawa et al. [22]. This method is based on measurements of absorbance of the pink-colored complex formed by thiobarbituric acid (TBA) and MDA using spectrophotometry at a high temperature (95°C) and 532-nm wavelength.

Total glutathione (tGSH) analysis

The amount of GSH in the total homogenate was measured according to the method of Sedlak and Lindsay with some modifications [23]. After tissue homogenization, supernatant was added for deproteinization at an equal volume (5 M metaphosphoric acid) and centrifuged at 3500 rpm for 2 min. The GSH level was determined using the top layer. 1500 μl of measurement buffer (200 mmol/l Tris-HCl buffer containing 0.2 mmol/l EDTA at pH 7.5), 500 μl supernatant, 100 μl 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) (10 mmol/l), and 7900 μl methanol were added to a tube and vortexed and incubated for 30 min at 37°C. DTNB was used as a chromogen and formed a yellow-colored complex with sulfhydryl groups. The absorbance was measured at 412 nm using a spectrophotometer (Beckman DU 500; Beckman Coulter, Brea, California, USA). The standard curve was obtained using reduced glutathione.

Glutathione reductase (GSHRd) activity analysis

GSHRd activity was determined spectrophotometrically by measuring the rate of nicotinamide adenine dinucleotide phosphate (NADPH) oxidation at 340 nm according to the method described by Carlberg and Mannervik [24]. After tissue homogenization, supernatant was used for GR measurement. After the NADPH and oxidized glutathione (GS(SG)) addition, the timer was started and absorbance was measured at 5 min intervals for 30 min at 340 nm.

Glutathione peroxidase (GPO) activity analysis

Glutathione peroxidase (GPO) activity was determined using the method described by Lawrence and Burk [25]. After tissue homogenization, the supernatant was used for GPO measurement. The mixture was incubated after adding monoperoxynitrate phosphate, ethylenediaminetetraacetic acid (EDTA), GSH, β-NADPH, sodium azide, and GSHRd. As soon as hydrogen peroxide (H₂O₂) was added, the timer was started and the absorbance at a 340-nm wavelength was recorded every 15 s for 5 min.

Nitric oxide (NO) analysis

Nitric oxide levels were measured using the Griess reaction, which is based on a two-step process. During the first step, nitrate is converted into nitrite by nitrate reductase. During the second step, nitrite reacts with the Griess reagent. This reaction formed a deep purple (violet) azo compound. The absorbance of this azo compound was measured photometrically at a 540-nm wavelength. This azo chromophore accurately determines nitrite concentrations as a marker of NO [26, 27].

Adrenaline content determination

The blood samples were placed into vacuum tubes with 2 ml of EDTA. These samples were then centrifuged at 3500 rpm for 5 min; the supernatant plasma samples were kept frozen at −80°C until the time of analysis. Measurements were carried out with a high-performance liquid chromatography (HPLC) device (Agilent 1100, Germany) using a commercial kit (Catecholamines in Plasma/Reagent kit for HPLC; Chromsystems Instruments & Chemicals GmbH, Gräfelfing, Germany).

Creatine kinase-MB assay

Creatine kinase-MB (CK-MB) in plasma obtained from animals was measured on a Roche/
while no statistically significant difference was found among the KTSA, KTA, and UCG groups. The levels of tGSH, GSHRd, and GPO were significantly lower in the striatum tissues of the K-30, K-60, T-15, and T-30 groups than in the UCG ($p < 0.001$), while these levels were almost the same in KTSA and KTA groups. The amount of NO was significantly lower in the striatum for the K-30 and K-60 groups compared to UCG ($p < 0.001$), and significantly higher in the T-15 and T-30 groups ($p < 0.005$). However, the amount of NO in the KTSA and KTA groups was similar to that of the control group (UCG).

Figure 2 shows the biochemical findings in the heart tissue. The level of MDA was significantly higher ($p < 0.001$) and the levels of tGSH, GSHRd, and GPO significantly lower ($p < 0.005$) in the heart tissues of the K-30, T-15, K-60 and T-30 groups compared to the UCG. Conversely, levels for all of these biochemical parameters were found to be similar among the KTSA and KTA groups and the control group (UCG). The amount of NO was significantly lower in the K-30 and K-60 groups than in the UCG ($p < 0.001$), but it was significantly higher in the T-15 and T-30 groups than in the UCG ($p < 0.001$). Differences among the KTSA and KTA groups and the UCG were not statistically significant.

Figure 3 shows the biochemical findings in the bronchial tissues. The MDA level significantly increased in the bronchial tissues of the K-30, K-60, T-15 and T-30 groups compared to the UCG ($p < 0.001$). As with other tissues for which the selected parameters were tested, the values for MDA were similar among the KTSA and KTA groups and the UCG. Levels of tGSH, GSHRd, and GPO were significantly lower in the bronchial tissues of the K-30, K-60, T-15, and T-30 animal groups compared to the KTSA and KTA groups and the UCG ($p < 0.001$). While T-15 and T-30 were the groups in which NO levels were highest in the bronchial tissues ($p < 0.001$), the K-30 and K-60 groups were observed to have the lowest levels of NO ($p < 0.001$). No statistically significant differences were found among the KTSA and KTA groups and the UCG in terms of the level of NO in the bronchial tissues.

Figure 4 shows the levels of adrenaline measured in the blood samples collected from the tail veins of the rats. Serum CK activity was 1251 ± 5.5, 1270.5 ± 17, 886.8 ± 6.8, 1371.3 ± 13.3, 1344.5 ± 4.2, 905.3 ± 28.3 and 879.2 ± 17.5 U/l and serum CK-MB activity was 210 ± 10.7, 204.2 ± 11.1, 99.1 ± 5, 256.5 ± 5, 263.2 ± 13.1, 103.5 ± 7.7 and 95.5 ± 4.1 U/l in the K-30, T-15, KTSA, K-60, T-30, KTA, and UCG groups, respectively.

**Discussion**

In this study, the side effects of ketamine, thiopental, and KTC administered at subanesthetic concentrations.
The effects of ketamine and thiopental used alone or in combination on the brain, heart, and bronchial tissues of rats were biochemically investigated and evaluated in comparison with an untreated control group (UCG). Our experimental results indicate that the duration of anesthesia created by KTC was longer than that created with separate administration of ketamine or thiopental. This type of interaction observed between ketamine and thiopental is known as the synergy of potentiation [28]. This synergy between drugs in a general sense is utilized to obtain the desired pharmacological influence using smaller doses of drugs [28, 29]. Additionally, the present study uses measures of oxidant/antioxidant parameters such as MDA, NO, tGSH, and GSHRd. We assessed whether ketamine, thiopental, or KTC (the two drugs in combination) causes side effects in the brain, heart, and bronchi. In recent studies, the side effects of various aggressive factors on these tissues have been assessed with measurements of oxidants/antioxidants that are known as biochemical parameters [10, 30–32].

Figure 1. MDA, GPO, tGSH, and GSHRd levels in brain tissue (K-30, ketamine 30 mg/kg group; T-15, thiopental 15 mg/kg group; KTSA; ketamine 30 mg/kg + thiopental 15 mg/kg group; K-60, ketamine 60 mg/kg group; T-30, thiopental 30 mg/kg group; KTA, ketamine 60 mg/kg + thiopental 30 mg/kg group; UCG – untreated control group. N = 8 for each group), *p < 0.05, **p < 0.001
Oxidative stress is a condition in which there is an increase in oxidant and decrease in antioxidant parameters in the tissues [33]. Our experimental results demonstrate that the use of ketamine and thiopental at anesthetic and subanesthetic doses increased the amount of MDA, which is an oxidant, and decreased the levels of parameters such as tGSH, GSHRd and GPO, which are antioxidants. Ketamine at subanesthetic doses is known to increase oxidant parameters and decrease antioxidant parameters in the brain [9]. The striatum has proven to be one of the brain regions that is exposed to the highest amount of oxidative damage due specifically to the overproduction of catecholamines in this region [34, 35]. In our previous study, intraperitoneal injection of ketamine at doses of 15, 30 and 60 mg/kg increased the levels in the blood of adrenaline, noradrenaline, and dopamine in rats, but ketamine at an anesthetic dose (60 mg/kg) increased the amount of catecholamines to a greater degree than did subanesthetic doses (15, 30 mg/kg) [5], which likely resulted in the further increase...
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in the amount of oxidants in cells. Thiopental administered at subanesthetic and anesthetic doses leads to oxidative stress in the brain striatum, likely because of the suppressed production of adrenaline, which causes systemic hypotension and associated high-risk complications [18]. Published studies have shown that, unlike ketamine, thiopental suppresses release of catecholamines [36] and decreases the amount of adrenaline in rats even at subanesthetic doses [16]. Furthermore, it was reported that hyperalgesia occurred in the animals receiving thiopental alone, while analgesia was observed in the animals receiving thiopental combined with adrenaline.

Our experimental results indicate that KTC at subanesthetic and anesthetic doses prevented impairment of the oxidant/antioxidant balance in favor of oxidants in the striatum of rats; in addition, based on the literature, the protective effect of KTC on the striatum is thought to develop due to the release of catecholamines being stabilized by KTC. As is known, the use of ketamine in patients

Figure 3. MDA, GPO, tGSH and GSHRd levels in bronchial tissue (K-30, ketamine 30 mg/kg group; T-15, thiopental 15 mg/kg group; KTSA; ketamine 30 mg/kg + thiopental 15 mg/kg group; K-60, ketamine 60 mg/kg group; T-30, thiopental 30 mg/kg group; KTA, ketamine 60 mg/kg + thiopental 30 mg/kg group; UCG – untreated control group. N = 8 for each group), *p < 0.05, **p < 0.001
with cerebral ischemia has been restricted; however, the combination of ketamine and thiopental has been reported to create a protective effect on cerebral cortical neurons [37]. Furthermore, in this study we found that ketamine administered at anesthetic and subanesthetic doses decreased and thiopental increased the amount of NO compared to the untreated control and KTC groups. In the literature, adrenaline has been reported to inhibit the release of NO in macrophage cells [37]. Ketamine also is known to increase adrenaline levels. This information suggests that ketamine might reduce NO levels through the presence of adrenaline.

Despite their opposite effects on the release of catecholamines, ketamine and thiopental led to oxidative stress in the striatum of animals when used alone; this is explained by the fact that NO is a bioregulator molecule that plays a role in physiologic and pathophysiologic processes [38]. Dawson and Dawson have argued that overproduction of NO leads to neuronal damage. Although increased production of NO was expected to show a protective effect, another study found that NO has a negative impact with respect to neuronal damage [39, 40]. Overproduction of NO increases reactions with superoxide anions, causing the formation of cytotoxic peroxynitrite and leading to neurotoxic effects [12]. NO has one unpaired electron and hence is categorized as an oxidant; therefore, NO inhibitors and antioxidants show a protective effect in NO-induced neurotoxicity. Recent studies suggested that, among other influencing factors, renal ischemia, NO, and oxidative stress are involved in sympathetic activation associated with hypertension [41].

From our results, it can be understood that oxidant/antioxidant balance was changed in favor of oxidants in the ketamine group with high blood adrenaline levels. As stated above, sympathomimetic activity is considered responsible for the cardiotoxic effect of ketamine [13]. Sympathomimetic activity is known to increase proportionally to the elevation of adrenaline levels [10]. Previous studies have experimentally demonstrated that ketamine increased the level of endogenous adrenaline in a dose-dependent manner [5]. Adrenaline has been reported to induce oxidative stress-related myocardial infarction in rats [42]. Unlike ketamine, thiopental at anesthetic and subanesthetic doses decreased the amount of adrenaline. Oxidant/antioxidant balance was observed to change in favor of oxidants in heart tissue, which had low levels of adrenaline. However, no studies were found in the literature demonstrating that thiopental induces oxidative stress in heart tissue. Unlike ketamine, thiopental decreases the release of adrenaline, blood pressure, and cardiac pulse power [16, 17]. These negative effects (hypotension) increase the risk for myocardial infarction [18]. KTC did not induce oxidative stress in the heart tissue, supporting our theory of catecholamine proposed in the pathogenesis of the cardiotoxicity induced by ketamine and thiopental. NO levels in the heart tissue are decreased by ketamine and increased by thiopental, which could be shown as the cause of the different effects of these drugs on vascular tone. NO at physiological levels is known to regulate blood pressure and flow by relaxing the smooth muscles of the heart and vasculature [43], while increases in NO levels cause hypotension [44].

Ketamine and thiopental in anesthetic and subanesthetic doses increased the amount of MDA and decreased the levels of GSH, GSHrd, and GPO in the bronchial tissues as in the striatum and heart tissues, suggesting that both drugs caused oxidative stress in the bronchi. It has been reported in the literature that ketamine exerts a bronchodilatory effect by increasing adrenaline, while thiopental produces a bronchoconstrictor effect by decreasing adrenaline [14, 45]. Furthermore, adrenaline has been reported to inhibit the release of NO [37]. The levels of NO were increased in the ketamine groups and decreased in thiopental groups, showing that our results correlate with those found in the literature. NO is known to lead to bronchodilation by relaxing the smooth muscles [46]. However, NO may be the cause of inflammation observed in asthma [47]. Therefore, NO leads to increased blood flow in the bronchial circulation and airway edema [48]. Numerous studies have demonstrated that the release of NO in airways is increased in patients with asthma,
which is restored through therapy with steroids [47]. KTC protected oxidant/antioxidant and NO balance in the bronchial tissue, possibly due to the normal blood levels of adrenaline in these groups.

In conclusion, when used alone ketamine and thiopental at anesthetic and subanesthetic doses caused oxidative stress in the striatum, heart, and bronchial tissues through opposite mechanisms. No correlations were found between the anesthesia duration induced by ketamine and thiopental alone at anesthetic and subanesthetic doses and oxidant/antioxidant parameters. However, the difference between KTC anesthesia time and anesthesia duration in the groups administered ketamine and thiopental alone is reflected in various oxidant/antioxidant parameters. Conversely, combination of the anesthetic and subanesthetic doses of ketamine and thiopental eliminated the side effects of both drugs on these tissues, suggesting that more reliable and longer anesthesia could be achieved with KTC in clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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