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Effect of Subanaesthetic Dose of Ketamine on Lungs Histology of Wistar Rat

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Abstract: *The study examined the effects of subanaesthetic doses of ketamine on the histology of the lungs. Twenty (20) adult Wistar rats of average weight 180g were used for the study. They were assigned to five groups; A, B, C, D and E (n=4). Group A served as the control while B, C, D, and E served as the experimental groups. Group A received 0.1 ml of normal saline, Group B and C received 25mg/kg and 30mg/kg body weight of ketamine hydrochloride respectively for 5 days and Group D and E received 25mg/kg and 30mg/kg of ketamine hydrochloride respectively for7days. After administration of the drugs for the different durations, the rats were sacrificed by 50mg/kg thiopental sodium. Aortic perfusion was done and the lungs were collected and processed for routine histological technique for Haematoxylin and Eosin (H&E) staining method. Histological sections of the lungs obtained from the experimental groups showed presence of few alveolar cells, fibrous Interalveolar spaces, and binucleate alveolar cells. Ketamine decrease in number and binucleation of the alveolar cells of the lungs. The effects were dosage and duration dependent. In conclusion, ketamine administration affected the histological integrity of the lungs therefore; use of ketamine for non-medical reasons should be done with utmost caution.*

Keywords: *Ketamine, Subanesthetic, Lungs, Alveolar, Histology*

1. INTRODUCTION

Ketamine (ketamine hydrochloride) is an anaesthetic agent that has been used both in human and veterinary surgical procedures [1]. Pharmacologically, ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that also acts on other receptor sites such as the opioid receptors and monoamine transporters [2, 3]. It is used in research as a pharmacological model of depression and schizophrenia [4]. Ketamine has been on the top list of abused and recreational drugs across the various geographical locations [5]. Though it is now a controlled substance in many countries in the world due to its psychotropic properties, its use as a recreational drug has become a worldwide phenomenon. In addition, the risk of acute toxicity associated with ketamine use, has demonstrated pathological changes in the different organs of animal models and humans, including its toxicity on central nervous system (CNS), urogenital system, intestine, pancreas, adrenal gland, liver, heart and immune system [4].

The medico- legal uses of ketamine are in anaesthesia, management of obstructive airway diseases and asthma, bronchospasm, and pain [1, 6]. In general anaesthesia where ketamine is the primary anaesthetic management of the airway is critical to ensure proper exchange of gasses [3]. Hence, airway anatomical assessment and management had played an important role in monitoring anaesthetics performance. In this regard, ketamine had been described as "without equal" for its ability to preserve and protect airway reflexes and also sustains respiration during surgery [1, 7]. These translate into increase lung compliance and decrease airway resistance [1].

Although respiration has been frequently stimulated, severe depression of respiration or apnoea are likely to occur following rapid intravenous administration of high doses and prolonged administration of ketamine hydrochloride. Consequently, laryngospasm and other forms of airway obstruction have been observed during ketamine hydrochloride anaesthesia [3].These physiological and pharmacological effects might have adaptive or pathologic influences on the microanatomy of the lungs. In addition,

previous literature on the anaesthetic effect of ketamine on the histology of the lungs is also scarce. Hence, the present study was designed to examine the effect of the subanesthetic doses of ketamine on the lungs driven with the fact that these doses are most often abused by recreational drugs users.

2. MATERIALS AND METHODS

2.1. Injectable (Drugs) and Chemicals

Ketamine hydrochloride and thiopental sodium injections (Rotex Medica. Trittau. Germany) were procured from registered pharmacy store in Enugu, the doses of the drugs were selected based on data from literature and drug information leaflets. Analytical and standard graded reagents for histological techniques were purchased from registered and certified chemical dealers in Enugu, Nigeria.

2.2. Experimental animals

Twenty (20) adult wistar rats of both sexes, average weights of 180g and ages between 5-7 weeks were purchased from the animal house of the Department of Physiology, College of Medicine, University of Nigeria Enugu Campus and housed at the animal facility of the Department of Anatomy, Ebonyi State University, Abakaliki. Nigeria. The animals were housed in netted iron cages in groups of four (n=4) rats per cage and maintained under standard laboratory conditions (temperature 24±2 degree Celsius, with relative humidity of 50%, and $^{12}/_{12}$ hour light-dark cycle) for two weeks acclimatization period prior to the commencement of the experiment. The animals were allowed free access to feed (grower's mash) and water *ad libithum.*

2.3. Ethical statements

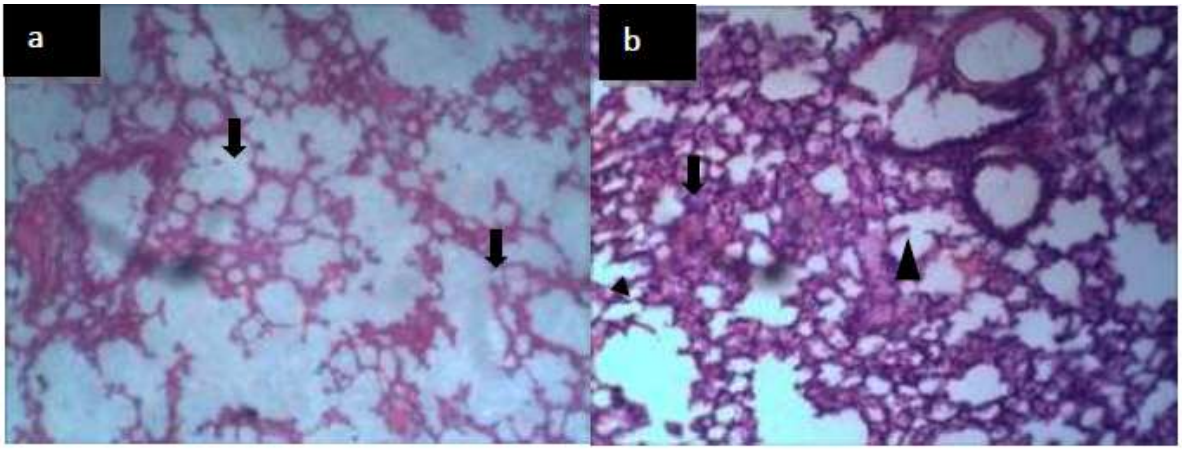
The experimental procedures and techniques used in the study were in accordance with acceptable principles for laboratory animal use and care by NIH, 1985 and EU directive of 1989:86/609/EEC [8]. All conditions and handling of the animals were approved by the Ethical Committee of Faculty Basic Medical Sciences, Ebonyi State University, Nigeria with the approval No 14409.

2.4. Experimental protocol

After the acclimatization period, at the age 7-9 weeks, the twenty (20) rats were randomized into control (group A, n=4) and experimental groups (B, C, D and E) each group having four (4) animals. Group A served as the vehicle. Groups B and C received 25mg/kg/bw and 30mg/kg/bw intraperitoneally (i.p) of ketamine hydrochloride respectively for 5 days, while Groups D and E received 25mg/kg/bw and 30mg/kg/bw (i.p) of ketamine hydrochloride consecutively for 7 days.

On the 8th day, rats in all the groups were euthanized with 50mg/kg/bw of thiopental sodium (Rotex Medica. Trittau. Germany) via intraperitoneal injection and aortic (transcardiac) perfusion was carried out with 4% paraformaldehyde. The lungs were carefully removed and fixed in 10% neutral buffered formal saline for 48hours. Thereafter, the tissues were processed for paraffin wax embedment. Serial sections of 10µm thickness were obtained using a rotary microtome. The deparaffinized sections were then stained using the Haematoxylin and Eosin (H & E) histological technique. The slides were analyzed and the micrographs were captured using research photographic microscope (Amscope 3.0 Model, England) at the Biotechnology centre, Ebonyi State University, Nigeria.

3. RESULTS



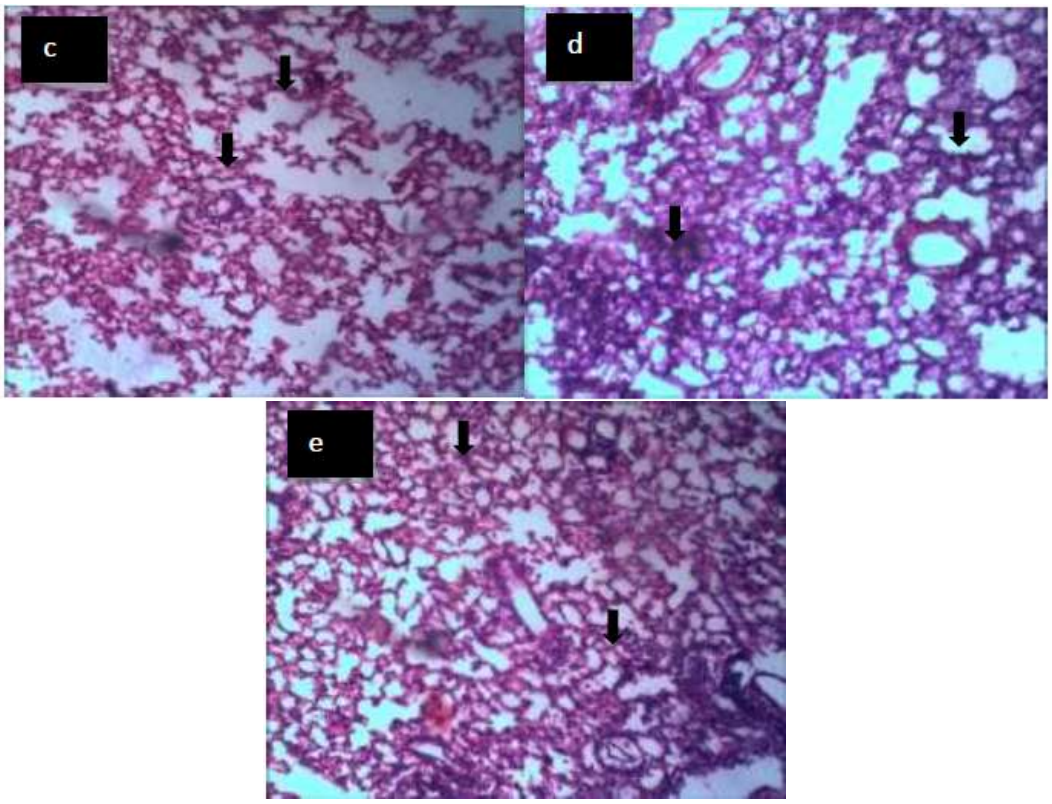


Figure1. *Photomicrograph of lungs section of rat (a) 0.1ml of normal saline (control) shows normal alveolar cells (arrows). (b) Ketamine (25mg/kg/5days) shows few alveolar Cells (arrow) and fibrous Interalveolar septa (arrow head). (c) Ketamine (30mg/kg/5days) shows sparse binucleate alveolar cells (arrows) (d) Ketamine (25mg/kg /7days) shows binucleate Alveolar Cells (e) Ketamine (30mg/kg/7days) shows fewer binucleate alveolar cells (arrows). H & E. x 200.*

4. DISCUSSIONS

The effect of subanaesthetic doses (25mg/kg/bw and 30mg/kg/bw) of ketamine hydrochloride at 5days and 7days on the lung tissue depicts dose and duration dependency. Normal histological features of the alveoli were observed in the control group (figure 1a), adjacent alveoli were connected by alveolar pores and separated by the alveolar septa. These pores help to equalize air pressure in adjacent alveoli. Similarly, administration of 25mg/kg/bw subanesthetic doses of ketamine for 5 days failed to reveal any histological defect rather few normal alveolar cells were found in the lungs section (fig 1b). In contrast, administration of 30mg/kg/bw/7days shows few alveolar cells which depicts adverse changes that might have led to the loss of some alveolar cells. Meanwhile, the seven days administration of 25mg/kg and 30mg/kg respectively revealed binucleated alveolar cells that were sparsely distributed.

Binucleated cells are known to contain two nuclei which can arise from variety of cause including cancer of the lung. The presence of these binucleated cells is suggestive of a dual mechanism: it may imply increase cell growth by multiple cell divisions. This can also be mimicked where adverse effects of an agent causes disintegration of adjacent cells membranes of adjoining septa or pores such that the two cells nuclei appear binuceated [9]. The resultant binucleation mechanism ultimately impact negative effect on cell viability and subsequent mitosis. Thus, the behaviour of these cells is similar to the characteristic of cells undergoing senescence showing binucleated cells with flat and enlarge morphology descriptive of replicative senescence [9, 10]

Several lines of evidences suggest that in human cells the physiological consequences of replicative senescence are to curtail tumorigensis and indirectly contribute to age-related pathologies including cancer [9]. Furthermore, these changes also suggest loss of alveolar cell viability and mitotic arrest thereby decreasing the number of alveolar cells which were supposed to line the surfaces of the alveoli. This plays causal role in the development of age-related pathology and in a number of chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) [11].

This indicates that, with longer duration of administration of ketamine, the binucleate cells will die off gradually, agreeing with previous findings that binucleated cells lose their viability [12] thereby leading pulmonary emphysema. This suggests that respiratory function of the lungs was adversely affected by consistent administration of ketamine for 7days with the high peak concentrations of ketamine after rapid injection. Finally, the pattern of changes indicates the ketamine effect was dose dependant, the degree of binucleation increased as dose and duration increase. The higher dose exerted major effect while it was also found to exhibit duration dependency at seven days of administration. These imply that single dose of ketamine as a preoperative anaesthetic may not have adverse effect but, repeated injection or recreational use can compromise lung histology and function.

5. Conclusion

The use of ketamine by recreational user can compromise lungs integrity which could result in respiratory disease via replicative senescence mechanisms. Thus the therapeutic intervention targeting such senescence can be considered for delayed or potentially to reverse the age-related respiratory changes that might accompany prolonged use or abuse of ketamine.

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