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Assessment of Three Anesthetics Used for Pulmonary Pharmacological Studies in Rats

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ABSTRACT

Experiments on pulmonary pharmacology are often performed in laboratory animals. Investigators collect organs, samples, or record modifications in the respiratory system during anaesthesia, which might significantly influence the data attained. Indeed, it is recommended to cautiously select the anaesthetic adapted for lung studies. This experiment aimed to evaluate three selected anaesthetics usually used in laboratory animal experiments, namely, (Zolite-rumpon (Z+R) mixture, halothane (HAL), and urethane (URE)) in rats. Rats were divided into four groups, control group, kept without treatment; Zolitel and Rumpon (Z+R) at a dose of 5 and 30 mg/kg body weight intraperitoneally, respectively; HAL group (5% with oxygen supply), and URE (1.5 mg/kg body weight) by inhalation. Blood samples were collected to determine the pH of the blood, bicarbonate (HCO_3^-), carbon dioxide partial pressure (pCO2), oxygen partial pressure (pO2), alveolar oxygen (A), saturated oxygen (O_2 Sat), magnesium (Mg^{2+}), calcium (Ca^{2+}), sodium (Na^+), potassium (K^+), and chloride (Cl^-) ions, haematocrit (Hct), and haemoglobin (Hb). The result indicates that the Z+R mixture causes slight to no differences in the measured data. At the same time, HAL and URE greatly reduced the blood pH and significantly disrupted the values of HCO3-, pCO2, pO2, A, and O2 Sat. Together, HAL and URE induced metabolic acidosis and respiratory depression. Hence, the Z+R mix is suitable for the three anaesthetics pulmonary pharmacology experiments.

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INTRODUCTION

Anaesthesia can be described as a condition of unconsciousness induced by reliable anaesthetics in order to achieve painless intervention in surgical operations **(Schwender *et al.*, 1995)**. Anaesthesia categorizes broadly into local or generalized **(Villablanca *et al.*, 2018)** and is accessible in many pharmaceutical forms, such as inhalational, intravenous, or intraperitoneal **(Noguchi *et al.*, 2019)**. In fact, without using anaesthesia, laboratory animals may suffer during experiments of inducing injury, disease models, or while harvesting organs, which is considered atrocious **(Anderson *et al.*, 2015, Cicero *et al.*, 2018)**.

Among these disease models, pulmonary experiments, such as acute lung injury (ALI) **(Zhu and Sun 2018)** and Chronic obstructive pulmonary disease (COPD) **(Ghorani *et al.*, 2017)**. The data derived from ALI and COPD may be highly affected by the anaesthetic used. Since the lung is the organ of interest, some anaesthetics cause the muscle to lose its tone, reduce gas exchange, cause respiratory depression, modify oxygen concentration and others **(Hedenstierna and Edmark 2015)**. Therefore, anaesthetics exploited in experiments of pulmonary pharmacology need to be selected with care to elude any confounding when the normal scope of data is required.

To induce general anaesthesia, numerous anaesthesia drugs are available. Among them is Zolitel-rumpon (Z+R) mixture, which is a Tiletamine-zolazepam combination administered by injection. Z+R mixture enables animals to go unconscious rapidly, smoothly, and for a long duration **(Janovsky *et al.*, 2000)**. Additionally, the Z+R mixture is believed to be safe and saves volume when applied in combination **(Coppola *et al.*, 2020)**. Halothane (HAL), as well, has been a frequently used anaesthetic in major operations for decades **(Mahboobi *et al.*, 2012)**. HAL is an inhalation anaesthetic popular for its safety and fast action **(Kangralkar and Jamale 2021)**. Regardless of these advantages, HAL causes liver injury **(Sheng *et al.*, 2018)** and lung and cardiac depression **(Tiscione and Rohrig 2021)**. Furthermore, Urethane (URE), ethyl carbamate, has been used extensively in animal experiments. However, URE has some drawbacks,

including lung cancer and liver toxicity **(Field and Lang 1988)**.

Several researchers reiterate numerous considerations when deciding on anaesthetic surgery, such as lung transplantation, lung resection, and bronchoscopy **(Pritchett *et al.*, 2021, Wang *et al.*, 2021)**. Most of these studies were carried out on human patients. Thus, this experiment was conducted to examine the effects of Z+R, the mixture, HAL, and URE on lung function using blood analysis and ascertain the appropriate option for lung experiments.

MATERIALS AND METHODS

Animal study design:

A total of 24 male Sprague Dawley rats (200-250) g were purchased from Samtako Bio Korea Co., Ltd., Daejeon, Korea. The rats were kept for acclimatization in a controlled environment with a 12 h light/dark cycle at 23±2°C and 50±5% humidity. The rats were freely accessed to feed and water. The animals were divided into 4 groups (6 rats/group), control (Cont) group without any anaesthetic but received 5 ml/kg normal saline; Z+R mix group, received Zolitel and Rumpon at 5 and 30 mg/kg B.W. intraperitoneally, respectively; HAL group, received halothane at 5% with oxygen supply by inhalation, and URE group, received urethane at a dose of 1.5 mg/kg B.W. intraperitoneally. The doses used in the study were selected based on a pilot study. All experimental protocols were approved by the Institutional Animal Ethics Committee and Committee on the Care of Laboratory Animal Resources at Chonbuk National University(CBU2013-0010) and performed with the Guidelines for the Care and Use of Laboratories.

Blood analysis:

For analyzing the levels of blood pH, bicarbonate (HCO_3^-), partial pressure of carbon dioxide (*p*CO2), partial pressure of oxygen (*p*O2), alveolar oxygen (A), saturated oxygen (O_2 Sat), magnesium (Mg^{2+}), calcium (Ca^{2+}), sodium (Na^+), potassium (K^+), and chloride (Cl^-) ions, haematocrit (HCT), and haemoglobin (H.B.), a fully automatic Nova Stat Profile R.T. (NOVA Biomedical Corp, Waltham, MA, USA) was used immediately after blood collection from the tail vein (approx. 1 ml) in lithium heparin tubes. HAL anesthesia was performed using an anaesthetic machine (Harvard Apparatus, Holliston, MA, USA).

Statistical analysis:

Statistical significance was analyzed using one-way variance analysis (ANOVA) with Bonferroni post-hoc evaluation for multiple group comparisons using GraphPad Prism 5.03 software (GraphPad Software Inc., San Diego, CA, USA). All data are reported as mean ± standard deviation of the mean (SEM). $P < 0.05$ was deemed statistically significant.

RESULTS

Effects of anaesthetic drugs on blood pH and gases:

To test the effects of the three anaesthetic agents on lung function, the levels of blood pH, HCO_3^-, pCO_2, pO_2, A, O_2 Sat in the blood were measured. The pH level decreased significantly in the HAL group compared to that of the Cont group. Even if the pH values have decreased in the Z + R and URE groups, the decrease is statistically non-significant compared to that of the Cont group, as illuminated in Figure 1. The HCO_3^- values diminished substantially in Z+E, HAL, and URE groups were in contrast to those in the Cont group. At the same time, the concentrations of pCO_2 elevated remarkably in only one group (HAL). However, the other two groups had an insignificant decline in the levels of pCO_2 in comparison to those of the control group (Fig. 1). This finding suggests that the three anaesthetics might suppress respiration and induce metabolic acidosis.

Figure 2 data shows that the values of pO_2 and A were ultimately diminished in all groups compared to those in the Cont group. However, the levels of O_2 Sat decreased considerably in the URE group compared with those of the Cont group, while Z+R and HAL showed a non-significant decline of the levels of O_2 Sat compared with those of the Cont group.

Effects of the three anaesthetic agents on blood ions, haemoglobin, and haematocrit:

Table (1) lists various changes in response to injection of the anaesthetics in rats. The Mg^{2+} and Ca^{2+} levels decreased in all groups vs. the Cont group; however, the Mg^{2+} and Ca^{2+} only noticeably reduced in the Z+R group and the URE group, respectively. Besides, the concentrations of Na^+, K^+ and Cl^- showed no significant differences against the control group except that the levels of K^+ and Cl in the HAL and URE groups, respectively, showed a considerable reduction matched to that of the Cont group. In addition, the Hct and Hb levels in all groups changed slightly compared to those in the control group, except for the Hct and Hb levels in the URE group, which raised drastically as opposed to those in the Cont group. These results reveal the three anaesthetics induced blood disorders.

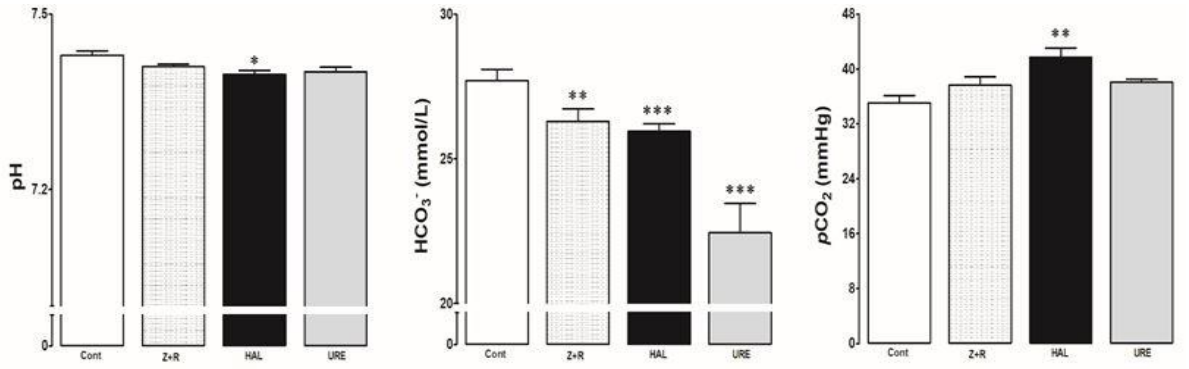

Fig. 1: Effect of zolitel-rumpon (Z+R) mix, halothane (HAL), urethane (URE) on blood pH, bicarbonate (HCO_3^-), and partial pressure of carbon dioxide (pCO_2). The data were reported as means±SD (n=6). *: $p<0.05$; **: $p<0.01$; and ***: $p<0.001$, Bonferroni *post hoc* test following one-way ANOVA control (Cont) vs. Z+R, HAL, and URE groups.

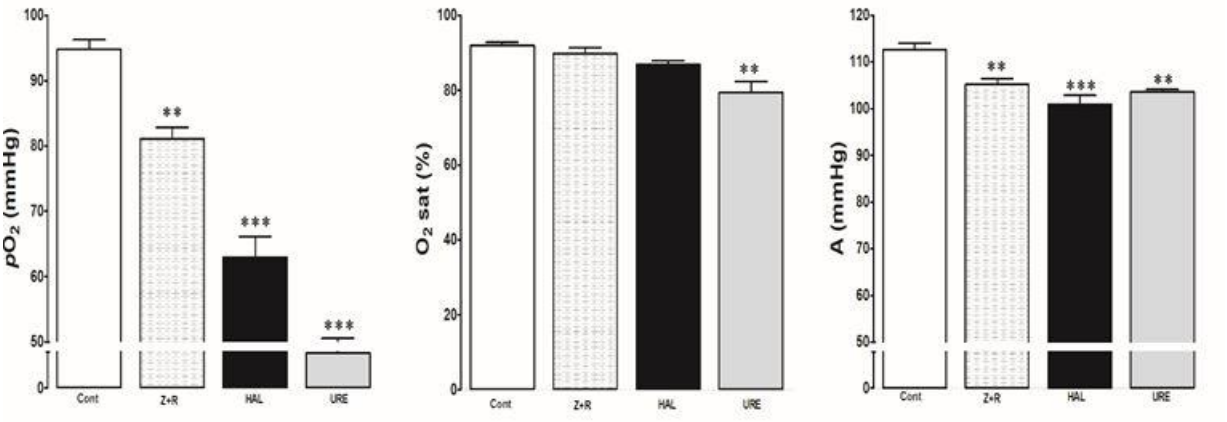

Fig. 2. Effect of zolitel-rumpon (Z+R) mix, halothane (HAL), urethane (URE) on the partial pressure of oxygen (pO_2), oxygen saturation (O_2 sat), and alveolar oxygen (A). The data were reported as means±SD (n=6). *: $p<0.05$; **: $p<0.01$; and ***: $p<0.001$, Bonferroni *post hoc* test following one-way ANOVA control (Cont) vs. Z+R, HAL, and URE groups.

Table 1: Effects of the zolitel-rump mixture, halothane, and urethane on blood ions, haematocrit, and haemoglobin:

	Cont	Z+R	HAL	URE
Mg^{2+} (mM/L)	0.52±0.02	0.47±0.02*	0.50±0.01	0.49±0.04
Ca^{2+} (mM/L)	1.36±0.3	1.33±0.4	1.28±0.04	1.24±0.10*
Na^{+} (mM/L)	141.5±1.1	139.8±0.9	141.2±1.0	141.4±0.9
K^{+} (mM/L)	4.96±0.67	4.95±0.32	4.00±0.07*	4.53±0.56
Cl^{-} (mM/L)	105.0±1.0	102.8±1.1	102.2±2.0*	106.0±1.5*
Hct (%)	41.6±3.8	40.4±1.4	40.2±2.1	46.2±2.8*
Hb (g/dL)	13.8±1.3	13.5±0.5	13.5±0.7	15.3±0.9*

The data are reported as means±SD (n=6). *: p<0.05. Bonferroni post hoc test following one-way ANOVA control (Cont) vs. zolitel-rumpon (Z+R) mix, halothane (HAL), urethane (URE) groups.

DISCUSSION

A lung function test can be carried out by measuring blood gas concentrations **(Cabrera Serrano and Rabinstein 2012)** and acid-base balance **(Helena *et al.*, 2015)**. Numerous studies examine the pharmacological properties of compounds on lung injuries **(Adam *et al.*, 2019b; Ali *et al.*, 2020)**. Substances, such as endotoxin, employed as a model for induction of pneumonia, generate blood acidosis i.e., lower pH **(Jobe *et al.*, 2000)**; in this case, if the investigator uses anaesthesia for euthanasia or sampling, the data attained might be exaggerated or compromised by anaesthetic being tested **(Hedenstierna and Rothen 2012)**.

In this study, the HAL and URE have profoundly affected the levels of pH and HCO_3^-, while rats in the Z+R group revealed data within the normal range (Figure 1). These results fit well with an earlier report **(Dardai and Heavner 1987)**. These parameters are often used to indicate acid-base balance **(Lee et al., 2002)**. A previous report outlined the effects of ketamine and xylazine on blood gases and showed that pH and HCO_3^- levels indicate blood acidosis **(Lei *et al.*, 2001)**. Also, **Dardai and Heavner (1987)** reported that HAL induces respiratory depression in rats, evidenced by an increment in blood carbon dioxide levels in the blood up to 48.42 mmHg, which agrees perfectly with our result (Figure 1).

Besides, our study indicates that urethane induces metabolic acidosis by decreasing the levels of blood pH, pO_2, O_2 sat HCO_3^-, and Ca^{2+} while increasing the levels of pH, pCO_2, and Cl, Hct, Hb, and A. These results are partly consistent with a consequence of a prior report testing the implications of urethane and isoflurane on blood gases. Acidosis induced by anaesthesia had been elucidated decades ago was believed to be owing to either low carbohydrate metabolism during unconsciousness **(Grint *et al.*, 2011)** or respiratory depression**(Gonzalez Castro *et al.*, 2017; Gupta *et al.*, 2018)**. It seems that the increased levels of Hct and Hb are due to hemoconcentration triggered blood sequestration into the peritoneum cavity. Halothane at a standard rate does not disturb respiration, but over time it induces respiratory depression **(Taiji *et al.*, 2021)**, which in turn interprets the alterations in blood gases and pH.

In an experiment in marine toads that examined the effects of anaesthesia on blood parameters, the haematocrit level increased to 2-folds although Hb had no effect **(Andersen and Wang 2002)**. However, it does not agree with the Hb levels that increased in HAL and URE groups **(Andersen and Wang 2002)** but agreed with an old study on the effects of ethyl urethane on hematocrit and blood pressure, which was explained by the loss of blood plasma **(Van Der Meer *et al.*, 1975)**. Effects of the three anaesthetics on the blood ions are negligible, possibly due to the short study time.

Z+R mixture has been used in various studies with little or no changes in blood parameters (Adam *et al.*, 2016; Adam *et al.*, 2018; Adam *et al.*, 2019a). Our data show that changes in the Z+R mix caused by anaesthesia all remained within the normal range. We attribute this benefit to the lower dose of each compound when used in combination compared to when used alone because using one compound requires an increase in the dose to obtain the desired effects, which might be associated with side effects. There are some limitations in this study, and we did not assess the impact of the three anaesthetics on the lung capacity of the air (spirometry) and the respiratory rate. In addition, this work did not examine the data after the animal returned to consciousness for comparison. This could be another line of investigation in further studies.

CONCLUSION

To sum up, HAL and URE eventually induced numerous disorders in the blood, comprising respiratory acidosis and falling oxygen levels, as opposed to heightened carbon dioxide levels in the blood. Z+R mixture is a comparatively good choice for experiments in the lung with minimal or no deviations in blood pH, gases, ions, and Hb concentration. Using Z+R mixture reduced the dose of each anaesthetic, which minimized their side effects if each was adopted individually.

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