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Research Paper

# Comparing Benzodiazepines-morphine-induced Respiratory Depression by Analyzing Respiratory Pattern in Rats

**Abbas Alimoradian[1], *Saeed Pazhoohan[2,3], Omid Mirzabeygi[2], Kiana Naderinia[1]**

1. Department of Pharmacology, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
2. Department of Physiology, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
3. Molecular and Medicine Research Center, Arak University of Medical Sciences, Arak, Iran.

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## ABSTRACT

**Background and Aim** Opioid and benzodiazepine family drugs are concurrently used in various patients. Considering the respiratory depressant effects of both classes, in this study, we investigated the effect of coadministration of morphine and several widely used benzodiazepines in the clinic on the rate of respiratory depression in rats.

**Methods & Materials** Seventy adult male Wistar rats were randomly divided into 10 groups; morphine, midazolam, diazepam, lorazepam, alprazolam, morphine-midazolam, morphine-diazepam, morphine-lorazepam, and morphine-alprazolam. Respiration signal was recorded using whole-body plethysmography 15 minutes after the intraperitoneal injection of the drugs. The respiratory pattern was examined using several parameters; the mean value of inter-breath interval and the respiratory rate, as well as the coefficient of variation and sample entropy analysis of inter-breath interval.

**Ethical Considerations** This study was approved by the Ethics Committee of Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1397.327).

**Results** Analyzing respiratory data revealed that injecting the anxiolytic dose of alprazolam, and the combination of morphine-alprazolam and morphine-midazolam, altered the respiratory pattern. Such changes were associated with a decrease in the number of breaths and an increase in the inter-breath interval in the explored test animals, compared with the controls. The obtained data also indicated that morphine-midazolam injection increased the variability of the breathing pattern; such an alternation was associated with increased irregularity and decreased coefficient of variation of the inter-breath interval.

**Conclusion** The present research results suggested that the short-term injection of morphine-midazolam changes the respiratory pattern more severely than morphine combined with other benzodiazepines.

## Extended Abstract

### 1. Introduction

Benzodiazepine and opioid family drugs are simultaneously prescribed in numerous clinical conditions [1]. In some cases, their concomitant use leads to impaired respiratory function [2]. The administration of opioids and benzodiazepines can lead to respiratory impairment; however, the respiratory effects of opioids and benzodiazepines can vary. For example, opioids, like morphine, in large amounts, can lead to respiratory failure and may require artificial ventilation [3]. In contrast to benzodiazepines, i.e. widely used in the clinical

* *Corresponding Author:*
**Saeed Pazhoohan, PhD.**
**Address:** Department of Physiology, School of Medicine, Arak University of Medical Sciences, Arak, Iran.
**Tel:** +98 (86) 34173520
**E-mail:** s.dpazhoohan@arakmu.ac.ir

settings [5, 6], dose-dependently impairs respiratory function [7]. However, in some clinical situations, there exists a need for the concomitant use of these drug families with few guidelines available for such practices. Therefore, this study aimed to compare the respiratory attenuation effect of the concomitant use of benzodiazepines plus morphine.

## 2. Materials and Methods

The animals used in this study were male Wistar rats in the weight range of 250-300 g. The study animals were maintained according to the ethical protocols of working with laboratory animals approved by the Arak University of Medical Sciences.

The examined animals were randomly divided into 10 experimental groups, as follows: 1- control, 2- morphine, 3- midazolam, 4- diazepam, 5- lorazepam, 6- alprazolam, 7- morphine-midazolam, 8- morphine-diazepam, 9-morphine-lorazepam, and 10-morphine-alprazolam. The anti-anxiety doses of midazolam (3 mg/kg) [5], diazepam (1 mg/kg), [8], lorazepam (0.5 mg/kg), [9], and alprazolam (2 mg/kg), [10], as well as an analgesic dose of morphine (10 mg/kg) [11] were injected intraperitoneally. Furthermore, normal saline was injected into the control animals.

Respiratory signals were recorded from conscious animals by animal-specific polytysmograph (BIODAC-R172, Trita Wavegram Co., Iran) [12]. On the day of registration, 15 minutes after injecting the drug into the research animals, a respiratory recording was performed. The recording time was 40 minutes per animal. In each explored animal, the mean intervals between respiration, the mean number of respirations, the coefficient of variation of intervals between respirations, and irregularities of intervals between respirations were evaluated.

## 3. Results

Examining respiration patterns among experimental groups signified that the mean number of respirations in alprazolam (P<0.01), midazolam-morphine (P<0.001), and alprazolam-morphine (P<0.001) groups was significantly lower than that in the control group. In the analysis of respiratory rate, no significant difference was observed between the groups receiving morphine adjunct to benzodiazepines (P>0.05) (Figure 1).

Examining the coefficient of variation of inter-respiratory intervals revealed that the coefficient of variation of intervals between respiration in the midazolam-morphine group presented a significant decrease, compared to the controls (P<0.01) (Figure 2).

Furthermore, the results of respiratory pattern irregularities indicated a significant difference between the control and midazolam-morphine groups (P<0.01). Additionally, the analysis of the results of respiratory pattern disorder provided a significant difference between the midazolam-

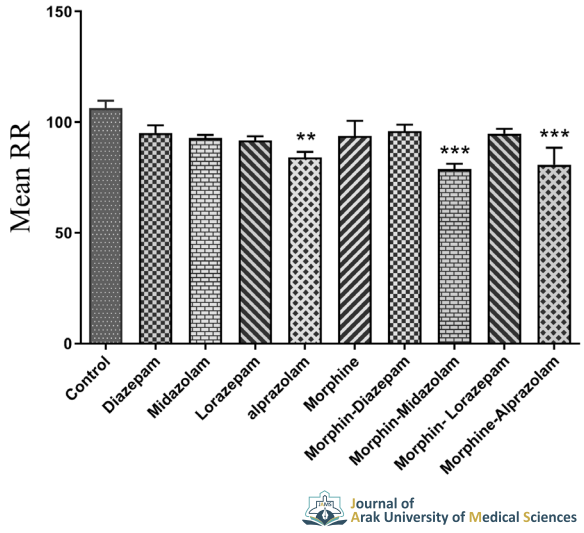


**Figure 1.** Comparing the mean number of breaths in the experimental groups

The obtained data were analyzed by one-way Analysis of Variance (ANOVA) and Tukey's post-hoc test, and illustrated as Mean±SEM. **P<0.01 and P<0.001, compared to the controls.

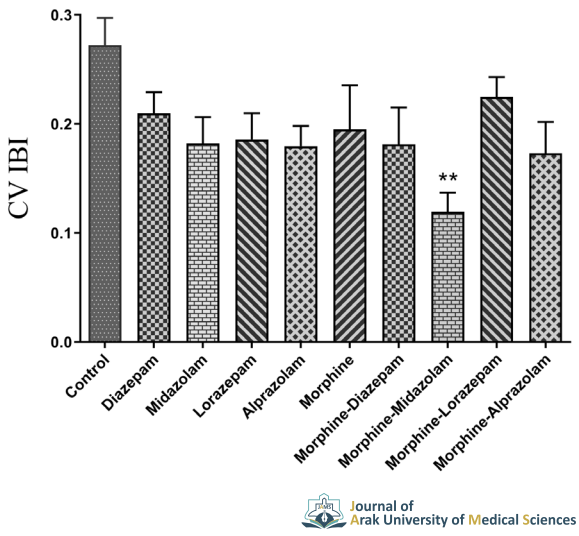


**Figure 2.** Comparing the coefficient of variation of inter-respiratory distances in the experimental groups

The obtained data were analyzed by one-way ANOVA and Tukey's post-hoc test and presented as Mean±SEM. **P<0.01, compared to the control group.

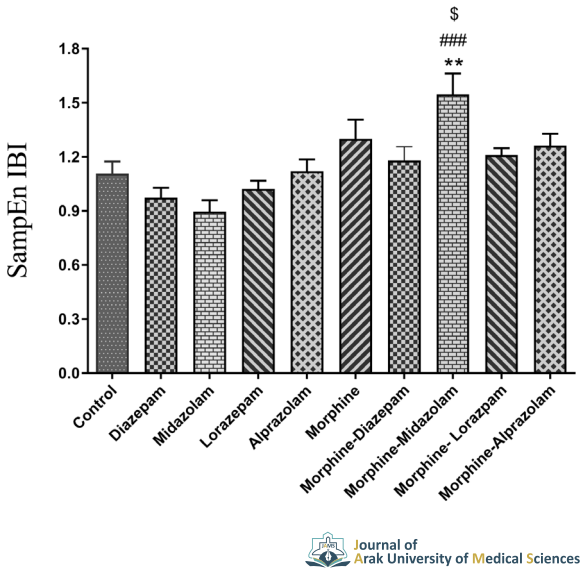


**Figure 3.** Comparing SampEn intervals between breaths in the experimental groups

The collected data were analyzed by one-way ANOVA and Tukey's post-hoc test and demonstrated as Mean±SEM. **P<0.01, compared to the controls; ###P<0.01, compared to the midazolam arm and P<0.01$ compared to the diazepam-morphine group. SampEn; Sample entropy.

morphine and diazepam-morphine groups (P<0.05). The pattern of respiration in the midazolam-morphine group significantly increased, compared to the midazolam group (P<0.001) (Figure 3).

## 4. Discussion and Conclusion

The present research results indicated that the combination of morphine-midazolam presents a more severe effect on respiratory patterns than the combination of other benzodiazepines with morphine. We also observed that injecting morphine into the explored animals did not impair respiration. One of the main complications of opioids is impaired respiratory function; however, this attenuation depends on the dose and speed of administration and how opioids are administered [18, 19]. The low and adjusted levels of opioids in patients were not associated with any serious clinical respiratory complications [20, 21]. Previous studies reported that injecting benzodiazepines impairs respiration [24, 25]. However, other studies documented no significant correlation between the low-dose injection of benzodiazepines to patients and severe respiratory adverse effects or alternations in blood gas pressure [27, 28, 29]. The present study results revealed that alprazolam injection significantly reduced the number of breaths. The difference in the respiratory effects of benzodiazepines might be attributed to the dose, the time of study of the effect, and the duration of using these medicines. Our results also highlighted that the effect of the respiratory attenuation of morphine-midazolam combination is greater than that of morphine adjunct to other benzodiazepines. The combined use of midazolam-morphine leads to impaired respiratory function [32]. This respiratory attenuation effect of the midazolam-morphine combination could be due to the cumulative effects of consuming midazolam plus morphine [33]. Midazolam is a short-acting, lipophilic benzodiazepine; it absorbs quickly and easily crosses the blood-brain barrier, leading to a rapid onset of drug action [34]. Evidence suggests that benzodiazepines increase the debilitating effects of the morphine-induced nervous system [35]. However, in the present study, injecting morphine adjunct to all benzodiazepines provided no change in the respiratory pattern. However, the nature of the interaction between benzodiazepines and morphine depends on the route of administration, the dose of the drug injected, and the timing of respiratory parameters [2].

## Ethical Considerations

### Compliance with ethical guidelines

This research was approved by the Ethics Committee of Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1397.327).

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### Authors' contributions

All authors met the standard writing criteria based on the recommendations of the International Committee of Medical Journal Publishers (ICMJP).

### Conflicts of interest

The authors stated no conflicts of interest.