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Chronopharmacological Study Of Angiotensin-Converting Enzyme Inhibitor Ramipril In Hypertensive Patients In A Hospital: Analysis Of Efficacy And Tolerability Based On Administration Time Variations

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ABSTRACT

This research investigates the chronopharmacological effects of Ramipril administration on hypertensive patients, focusing on the timing of drug intake. Studies conducted by Firli Choerun Nisa and Siti Rohmiati in 2022 provide the basis for this analysis. Using observational-analytic methods with cross-sectional designs, data were collected prospectively from 23 patients in each study. Firli Choerun Nisa's study at RSUD Singaparna Medika Citrautama, Tasikmalaya Regency, involved 14 patients in the light zeitgeber group and 9 in the dark zeitgeber group. Results indicated significant reductions in both systolic and diastolic blood pressures, with the dark zeitgeber group experiencing more substantial decreases. The SPSS analysis showed a p-value of 0.062, indicating no statistically significant difference between the groups. Siti Rohmiati's study at RSUD Dr. Soekardjo Tasikmalaya found similar results. The light zeitgeber group showed a systolic decrease of 9.9 mmHg and a diastolic decrease of 5 mmHg, while the dark zeitgeber group had decreases of 16.66 mmHg and 10.56 mmHg, respectively. The SPSS analysis also yielded a p-value of 0.062, supporting the conclusion of no significant difference in Ramipril's efficacy based on administration timing. The comprehensive analyses revealed that Ramipril effectively reduces blood pressure regardless of the administration time. Significant reductions in both the daytime and nighttime groups were noted, with trends suggesting a more pronounced effect during nighttime administration. These findings emphasize the importance of flexibility in medication timing, enhancing patient adherence without compromising therapeutic outcomes. In conclusion, the timing of Ramipril administration, whether in the morning or evening, does not significantly impact its effectiveness in managing hypertension. This flexibility offers practical benefits for clinical practice, supporting better patient adherence and optimized hypertension management. These studies contribute to the broader understanding of chronopharmacology, providing insights for improved treatment strategies in hypertensive care.

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INTRODUCTION

Hypertension is one of the most common chronic medical conditions globally, significantly contributing to cardiovascular morbidity and mortality (Mills, K. T., 2020). Often referred to as the "silent killer," this disease typically shows no clear symptoms until serious complications such as coronary heart disease, stroke, and kidney failure arise (Carey, R. M., 2022). Effective management of hypertension is crucial in preventing these complications and enhancing patients' quality of life (Brouwers, S., 2021). A primary approach in treating hypertension involves the use of antihypertensive drugs, including Angiotensin-Converting Enzyme (ACE) inhibitors like Ramipril (Komilovich, E. B., 2024).

Ramipril is a widely used ACE inhibitor in hypertension treatment. It functions by inhibiting the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that raises blood pressure (El Mokadem, M., 2020). By reducing the levels of angiotensin II, Ramipril helps lower blood pressure and decreases the workload on the heart (Motrapu, M., 2020). Additionally, Ramipril has protective effects on the kidneys, which is particularly beneficial for patients with chronic kidney disease (Saristiana, Y., 2023).

The effectiveness and tolerability of Ramipril can be influenced by various factors, including the timing of its administration (Prasetyawan, F., 2024). Chronopharmacology, the study of how the timing of drug administration affects its efficacy and tolerability, has become increasingly important in hypertension management (Nisa, F. C., 2024). Research indicates that human blood pressure exhibits diurnal variation, peaking in the morning and declining at night. This variation can affect how antihypertensive drugs work, and thus, the timing of drug administration can significantly impact therapeutic outcomes (Mawarni, O. I., 2024).

Chronopharmacological studies have shown that administering antihypertensive drugs at different times of the day can yield different effects (Setiya, A., 2009). For instance, some studies suggest that taking ACE inhibitors at night may provide better blood pressure control and reduce cardiovascular events compared to morning administration. However, these findings require further validation through more extensive and in-depth research (Turner, J. M., & Kodali, R., 2020).

This study aims to evaluate the impact of Ramipril administration timing on its efficacy and tolerability in hypertensive patients in a hospital setting (Cutrell, S., 2023). By analyzing data from patients who receive Ramipril at different times of the day, this research hopes to provide new insights into how optimizing drug administration timing can improve therapeutic outcomes for hypertensive patients (Ahmad, H., 2023). Additionally, this study will assess potential side effects arising from varying administration times, which is crucial for ensuring patient safety and comfort (Prasetyawan, F., 2024).

The results of this study are expected to make significant contributions to clinical practice in hypertension management (Nababan, O. A., 2024). By better understanding how the timing of Ramipril administration affects its efficacy and tolerability, doctors can make more informed decisions about drug regimens, thereby improving blood pressure control and reducing the risk of cardiovascular complications (Park, H. S., 2024). Moreover, this research

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could pave the way for further studies in the field of chronopharmacology, particularly concerning hypertension treatment (Marjot, T., 2022).

This study not only holds high scientific value but also significant clinical relevance. Implementing the findings from this research is anticipated to enhance the quality of life for hypertensive patients through more effective and safe management (Fujimura, A., & Ushijima, K., 2023). This study also underscores the importance of an individualized approach in treatment, considering specific factors like the patient's biological rhythms in designing optimal therapeutic strategies.

METHODS

This study employs a narrative method, where this approach is conducted by studying one or more individuals to obtain comprehensive narrative reports. The narrative method was chosen because it allows researchers to deeply explore individual experiences and understand the context and dynamics behind the phenomena being studied. This approach is particularly suitable for research that requires an in-depth understanding of the subject, such as in the chronopharmacological study of Ramipril use in hypertensive patients.

The data collection technique used in this research is a literature review. A literature review involves collecting data by seeking information from published sources, such as scientific journals and reference books. This technique was chosen because it enables researchers to access various perspectives and findings relevant to the research topic. By gathering data from existing sources, researchers can build a strong theoretical foundation and support the analysis of the collected narrative data.

To gather relevant data, this study uses the Google Scholar search engine with the keywords "chronopharmacology" and "ramipril." Google Scholar was chosen because it is one of the most comprehensive search engines for academic literature, allowing researchers to access various scientific journals, articles, theses, books, and other academic publications. Using the keywords "chronopharmacology" and "ramipril," researchers can focus the search on studies directly related to the research topic.

From the search results using these keywords, the researchers identified two primary studies that are the focus of the analysis: the studies by Siti Rohmiati (2022) and Firli Choerun Nisa (2022). These two studies were selected because they provide deep and relevant insights into the use of Ramipril in the context of chronopharmacology, which is the core of this research. The study by Siti Rohmiati (2022) explores the effect of the timing of Ramipril administration on its efficacy and tolerability in hypertensive patients. This study provides important empirical data on how diurnal variations in blood pressure affect drug performance, as well as the clinical implications of adjusting the timing of drug administration. The data obtained from this study provide a strong basis for understanding the chronopharmacological context of Ramipril use. The study by Firli Choerun Nisa (2022) also focuses on the chronopharmacological aspects of Ramipril use. This study examines various factors influencing the effectiveness of Ramipril, including the timing of drug administration, and evaluates the clinical outcomes of patients receiving Ramipril at different times of the day.

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The findings from this study provide additional insights into how optimizing the timing of drug administration can improve blood pressure control and reduce the risk of cardiovascular events.

By combining the findings from these two studies, the researchers can develop a more comprehensive understanding of the role of chronopharmacology in managing hypertension using Ramipril. The narrative data from this research is expected to provide new insights that can be used to enhance clinical practice and offer more precise recommendations regarding the timing of Ramipril administration. Throughout the research process, the researchers also conducted a critical evaluation of the collected literature, considering the quality and relevance of the identified studies. The researchers assessed the methodology, sample, and findings of each study to ensure that only the most relevant and high-quality information was used in the analysis. This approach helps ensure that the conclusions drawn are based on solid and reliable data.

The narrative method used in this research allows the researchers to compile reports that depict patients' experiences in detail and contextually. Thus, this research not only presents statistical data but also provides a rich narrative about how patients respond to Ramipril treatment within the chronopharmacological context. This approach aids in understanding the complexity and variability in patients' responses to treatment, which is often not fully captured by quantitative methods. The entire research process, from literature search to data analysis, is designed to provide a deep and holistic understanding of the use of Ramipril in hypertension treatment. The results of this research are expected to make significant contributions to the chronopharmacology literature and assist physicians in designing more effective and safe treatment strategies for hypertensive patients. By better understanding how the timing of Ramipril administration affects its efficacy and tolerability, this research aims to improve the quality of care and clinical outcomes for patients.

RESULTS AND DISCUSSION

The study conducted by Firli Choerun Nisa in 2022, titled "Chronopharmacology Study of Ramipril Usage in Hypertensive Patients at RSUD Singaparna Medika Citrautama, Tasikmalaya Regency," serves as the foundation for this research. The timing of drug administration in this study is divided into two distinct periods: the light zeitgeber (06:00-18:00) and the dark zeitgeber (18:00-06:00). The research employed an observational analytical method with a cross-sectional design. Data collection was conducted prospectively from February to May 2022, involving a total of 23 patients. These patients were categorized into two groups: 14 patients who took Ramipril during the light zeitgeber and 9 patients who took it during the dark zeitgeber.

The study aimed to evaluate the differences in the effectiveness of Ramipril administration based on the timing of the drug intake. The results demonstrated a notable decrease in both systolic and diastolic blood pressures in both groups. Specifically, in the group that took Ramipril during the light zeitgeber, there was an average reduction of 9.9 mmHg in systolic blood pressure and 5 mmHg in diastolic blood pressure. Conversely, the

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group that took the medication during the dark zeitgeber experienced a more substantial decrease, with an average reduction of 16.66 mmHg in systolic blood pressure and 10.56 mmHg in diastolic blood pressure.

To analyze these results, the researchers utilized the Statistical Package for the Social Sciences (SPSS) software. The analysis aimed to determine whether the differences in blood pressure reduction between the two groups were statistically significant. The p-value obtained from the SPSS analysis was 0.062, which is greater than the commonly accepted threshold of 0.05. This indicates that the observed differences in blood pressure reduction between the light and dark zeitgeber groups were not statistically significant. The conclusion drawn from this study is that the timing of Ramipril administration, whether during the light or dark zeitgeber, does not significantly affect its efficacy. Both timing periods provide similar effectiveness in reducing blood pressure among hypertensive patients. This finding is crucial for clinical practice, as it suggests that the flexibility in the timing of Ramipril administration can be maintained without compromising its therapeutic benefits. Patients can take Ramipril either in the morning or at night based on their convenience and lifestyle, without worrying about a significant difference in treatment outcomes.

The choice of an observational analytical method with a cross-sectional design was appropriate for this study, as it allowed the researchers to observe and compare the effects of Ramipril administration at different times of the day within a relatively short period. The prospective data collection approach ensured that the data was current and relevant, providing an accurate picture of the drug's effectiveness based on administration timing. The involvement of 23 patients, although a small sample size, provided sufficient data to conduct preliminary analyses and draw meaningful conclusions. Future studies could benefit from larger sample sizes to further validate these findings and enhance the generalizability of the results. Additionally, a longer study period and more diverse patient demographics could provide a more comprehensive understanding of how chronopharmacological factors influence Ramipril's efficacy.

The significant reductions in both systolic and diastolic blood pressures in the dark zeitgeber group, compared to the light zeitgeber group, although not statistically significant, indicate a trend that could be explored further. This trend suggests that nighttime administration might have a slightly more pronounced effect on blood pressure reduction. Understanding the underlying mechanisms and potential benefits of nighttime administration could lead to more tailored and effective hypertension management strategies. Firli Choerun Nisa's 2022 study provides valuable insights into the chronopharmacological aspects of Ramipril usage in hypertensive patients. The findings support the notion that the timing of Ramipril administration can be flexible without significantly affecting its efficacy. This flexibility can enhance patient adherence to medication regimens and ultimately improve hypertension management. The study underscores the importance of considering individual patient needs and lifestyle factors in the clinical decision-making process, ensuring that treatment plans are both effective and convenient for patients.

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Based on the research conducted by Siti Rohmiati in 2022 titled "Chronopharmacological Study of Ramipril Use in Hypertensive Patients at RSUD Dr. Soekardjo Tasikmalaya," the timing of medication administration was divided into two periods: light zeitgeber (06:00-18:00) and dark zeitgeber (18:00-06:00). The research employed an observational-analytic method using a cross-sectional design, with data collected prospectively from February to May 2022. The study involved 23 patients, with 14 patients in the light zeitgeber Ramipril group and 9 patients in the dark zeitgeber Ramipril group. The results indicated that patients experienced a systolic decrease of 9.9 mmHg and a diastolic decrease of 5 mmHg in the Ramipril group taken during the light zeitgeber. In contrast, the dark zeitgeber group showed a systolic decrease of 16.66 mmHg and a diastolic decrease of 10.56 mmHg. According to the SPSS analysis, the p-value for Ramipril use during light and dark zeitgebers was 0.062 ($p > 0.05$), leading to the conclusion that Ramipril's effectiveness was similar whether taken in the morning or evening.

The study used an observational method with an analytic design and a cross-sectional research design. Data were collected prospectively, including examination results and medical records of hypertensive patients, along with interviews involving 18 patients. According to the SPSS analysis, the reduction in blood pressure for the Ramipril group during the daytime was 19.18/7.82 (59.2%) with p-values of 0.001 and 0.092. Additionally, the nighttime Ramipril group showed a blood pressure reduction of 35.29/5.85 (83.4%) with p-values of 0.013 and 0.012. These results indicate that there was no significant difference in the effectiveness of Ramipril between the dark and light zeitgeber groups among the 18 hypertensive patients at RSUD Dr. Soekardjo Tasikmalaya.

The methodology of this research involved a thorough and detailed approach to understanding the impact of timing on the administration of Ramipril, a commonly used antihypertensive medication. By dividing the administration times into light and dark zeitgebers, the study aimed to assess the potential differences in drug efficacy and tolerability based on the circadian rhythm of the patients. The observational-analytic method and cross-sectional design were crucial in capturing the variations and outcomes within a specific period, allowing for a comprehensive analysis of the collected data.

Prospective data collection was essential in ensuring the accuracy and reliability of the study results. This method involved gathering data in real-time from the patients, which included their medical examinations and records, as well as conducting interviews to gain further insights into their experiences and responses to the medication. By involving 23 patients and analyzing their blood pressure readings before and after the administration of Ramipril, the study provided valuable information on the medication's performance during different times of the day.

The use of SPSS for data analysis was instrumental in determining the statistical significance of the findings. The p-value obtained from the analysis (0.062) indicated that there was no significant difference in the effectiveness of Ramipril between the light and dark zeitgeber groups. This finding is important as it suggests that the timing of Ramipril

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administration, whether in the morning or evening, does not significantly impact its efficacy in reducing blood pressure in hypertensive patients.

The detailed analysis of blood pressure reduction in both the daytime and nighttime groups provided additional insights into the medication's performance. The significant reductions observed in both groups (19.18/7.82 during the daytime and 35.29/5.85 during the nighttime) highlight Ramipril's effectiveness in managing hypertension regardless of the administration time. The differences in the p-values for the reductions (0.001 and 0.092 for daytime, 0.013 and 0.012 for nighttime) underscore the importance of considering individual variations and responses in clinical practice. This research contributes to the understanding of chronopharmacology and its implications for hypertensive treatment. The findings suggest that the timing of Ramipril administration does not significantly affect its efficacy, providing flexibility for patients and healthcare providers in managing hypertension. The study's methodology, involving a comprehensive and detailed analysis of patient data and blood pressure readings, ensures the reliability and relevance of the conclusions drawn.

The research by Siti Rohmiati in 2022 on the chronopharmacological use of Ramipril in hypertensive patients at RSUD Dr. Soekardjo Tasikmalaya provides significant insights into the impact of medication timing on efficacy. The observational-analytic method, cross-sectional design, and prospective data collection were critical in capturing accurate and reliable data. The use of SPSS for statistical analysis confirmed that there is no significant difference in the effectiveness of Ramipril between light and dark zeitgebers. These findings contribute to the broader understanding of chronopharmacology in hypertensive treatment and offer practical implications for optimizing medication administration to improve patient outcomes.

CONCLUSION

The studies conducted by Firli Choerun Nisa and Siti Rohmiati in 2022 provide valuable insights into the chronopharmacological aspects of Ramipril usage in hypertensive patients. Both studies explored the impact of medication timing, dividing administration periods into light zeitgeber (06:00-18:00) and dark zeitgeber (18:00-06:00). Utilizing observational-analytic methods with a cross-sectional design, data were collected prospectively, ensuring the accuracy and relevance of the findings.

In Firli Choerun Nisa's study at RSUD Singaparna Medika Citrautama, Tasikmalaya Regency, 23 patients were involved, with 14 in the light zeitgeber group and 9 in the dark zeitgeber group. The results showed significant reductions in both systolic and diastolic blood pressures for both groups, with the dark zeitgeber group experiencing a more substantial decrease. The statistical analysis using SPSS revealed a p-value of 0.062, indicating no significant difference in efficacy between the two groups. Similarly, Siti Rohmiati's study at RSUD Dr. Soekardjo Tasikmalaya involved 23 patients, with comparable findings. The light zeitgeber group saw a systolic decrease of 9.9 mmHg and a diastolic decrease of 5 mmHg, while the dark zeitgeber group experienced decreases of 16.66 mmHg and 10.56 mmHg,

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respectively. The SPSS analysis yielded a p-value of 0.062, supporting the conclusion that the timing of Ramipril administration does not significantly impact its effectiveness.

The detailed analyses in both studies showed that Ramipril is effective in reducing blood pressure regardless of the time of administration. In Firli Choerun Nisa's study, the daytime group had reductions of 19.18/7.82 (59.2%) with significant p-values, and the nighttime group had reductions of 35.29/5.85 (83.4%) with significant p-values. These results suggest that while nighttime administration might show a trend of more pronounced effects, the overall efficacy remains comparable. The use of prospective data collection and the comprehensive analysis of patient responses in both studies underscore the robustness of the findings. These studies highlight the importance of considering individual patient needs and lifestyles in clinical practice, as the timing flexibility in Ramipril administration can enhance patient adherence to medication regimens without compromising therapeutic outcomes.

In conclusion, the research conducted by Firli Choerun Nisa and Siti Rohmiati demonstrates that the timing of Ramipril administration, whether in the morning or evening, does not significantly affect its efficacy in managing hypertension. This flexibility in medication timing is crucial for clinical practice, offering convenience for patients and supporting better adherence to treatment plans. The findings contribute to the broader understanding of chronopharmacology and provide practical implications for optimizing hypertension management to improve patient outcomes.

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