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Biorhythm Analysis Of The Analgesic Effect Of Paracetamol In Inpatients With COVID-19 At The Hospital

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ABSTRACT
The global COVID-19 pandemic has posed unprecedented challenges to global health, impacting healthcare institutions worldwide. Dr. Soedomo Regional General Hospital in Trenggalek has been actively involved in treating COVID-19 patients, emphasizing the need for improved care standards and effective symptom management. Paracetamol, a commonly used medication, is a key focus in this endeavor. This study investigates the chronopharmacology of paracetamol in COVID-19 patients, emphasizing the importance of timing in therapeutic interventions. The research, conducted at Dr. Soedomo Regional General Hospital, involves 100 COVID-19 patients undergoing paracetamol therapy. The analysis includes demographic data, paracetamol administration at different times, and the resulting body temperature changes. The findings reveal that the body's response to paracetamol varies significantly depending on the time of administration. Notably, at 4:00 PM, a more pronounced decrease in body temperature is observed, suggesting a heightened effectiveness of therapy. This phenomenon is attributed to the body's circadian rhythm, influencing physiological functions over a 24-hour period. This study lays the groundwork for the "right time, right dose" concept in clinical practice. Considering the circadian rhythm is essential in designing personalized and effective treatment protocols, aiming for optimal outcomes. Despite limitations, including a small sample size, this research provides valuable insights into the circadian aspects of drug efficacy, paving the way for more tailored treatment approaches.

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INTRODUCTION

The global COVID-19 pandemic that has swept across the world has presented unprecedented challenges to global health. Dr. Soedomo Regional General Hospital in Trenggalek, as a healthcare entity involved in the treatment of COVID-19 patients, has witnessed a long journey in responding to and caring for individuals infected with the SARS-CoV-2 virus (Prasetyawan, F., 2023). In an effort to continually improve care standards and understanding of symptom management, the use of medications, such as paracetamol, has been a primary focus (Smith, J., 2020).

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The worldwide COVID-19 pandemic has exposed various complexities and challenges in managing patients infected with the SARS-CoV-2 virus. Since the onset of the COVID-19 pandemic, healthcare services worldwide have faced significant challenges in responding to and treating patients infected with the SARS-CoV-2 virus. Dr. Soedomo Regional General Hospital in Trenggalek, as a healthcare entity actively involved in the treatment of COVID-19 patients, continues to strive for an improved understanding and approach to effective and safe patient management. In this context, the use of paracetamol has become one of the main strategies to address symptoms such as fever and pain in COVID-19 patients (Saristiana, Y., 2023).

Paracetamol, or acetaminophen, is one of the commonly used drugs to alleviate fever and reduce pain. However, its less-focused use in terms of timing within the context of chronopharmacology creates the potential to enhance treatment effectiveness and provide a deeper understanding of how the body's biological rhythms can influence drug responses (Akhmal, F., 2024). Consequently, the current limitations in knowledge regarding how paracetamol interacts with the body's circadian cycles, especially in COVID-19 patients, form a strong basis for further research (Brown, A., 2021).

Chronopharmacological analysis of paracetamol use in COVID-19 patients can offer profound insights into how the timing of drug administration can affect the body's response to treatment. There is evidence that the body's circadian rhythm can influence the metabolism and pharmacological effects of a drug. Differences in paracetamol response based on the timing of administration, particularly considering the potential variations in circadian rhythms in hospitalized COVID-19 patients, may open the path to improved therapy effectiveness, reduced side effects, and a better understanding of the pharmacological dynamics of paracetamol in this specific patient population. Although the general use of paracetamol is widely recognized, the chronopharmacological perspective, which examines the relationship between drug administration timing and biological body responses, has not been fully explored. The body's circadian rhythm is known to influence the mechanisms of metabolism and pharmacological responses to a drug (Johnson, M., 2019).

Chronopharmacological analysis of paracetamol use in COVID-19 patients at Dr. Soedomo Regional General Hospital in Trenggalek aims to provide a deep understanding of how the timing of drug administration can affect therapeutic responses. Through this research, it is hoped that valuable information can be discovered to guide clinical decisions related to the use of paracetamol, thereby improving treatment effectiveness, reducing side effects, and detailing more personalized treatment guidelines (Anderson, R., 2022). By understanding the chronopharmacological aspects of COVID-19 patients in more detail, it is expected to pave the way for improving more precise and tailored treatment strategies based on individual biological characteristics.

This study aims to analyze the chronopharmacology of paracetamol use in COVID-19 patients at Dr. Soedomo Regional General Hospital in Trenggalek, with a focus on the body's biological response to the drug at various time points within the 24-hour cycle. With a deeper understanding of how the timing of paracetamol administration affects

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therapeutic effects and tolerability, it is hoped that this research can provide a solid scientific foundation for the development of more personalized treatment guidelines (Davis, S., 2021).

Research on chronopharmacology has become an essential aspect in understanding drug use, especially in the context of specific health conditions such as COVID-19 infection. Studies related to the chronopharmacological analysis of paracetamol use in COVID-19 patients at Dr. Soedomo Regional General Hospital in Trenggalek are relevant research topics to delve deeper into the impact of biological timing on the effectiveness and tolerability of drugs.

Research has shown that circadian rhythms play a significant role in the body's immune response to infections. Given that COVID-19 has systemic effects involving the immune response, chronopharmacological studies on paracetamol use can provide insights into how the timing of drug administration can influence the reduction of fever and other symptoms in COVID-19 patients. Previous research has also highlighted the role of circadian rhythms in drug pharmacokinetics, and this analysis can provide a basis for optimal paracetamol dosage adjustments at various times for COVID-19 patients.

Chronopharmacology is a field of study that explores how the effects of drugs may vary with the biological and endogenous periodic time. Biological functions, including cardiovascular functions such as the heart and blood vessels, exhibit circadian rhythms reflecting changes in activity over a 24-hour period (Wilson, C., 2018). Epidemiological studies show that the risk of cardiovascular problems such as angina, myocardial infarction, and stroke tends to be higher in the morning (Foster & Kritzman, 2004). The circadian cycle is a repetitive process from light to dark that occurs every 24 hours, and most species living on Earth have adapted to regular changes in their surrounding environment. Biological rhythms in the body, including sleep patterns, adapt and synchronize with the circadian cycle. For example, body temperature changes follow a specific pattern, reaching its peak in the afternoon, gradually decreasing as evening approaches, and dropping significantly during sleep (White, L., 2020). Understanding chronopharmacology allows us to better comprehend how biological timing influences the body's responses to medications, particularly in the context of cardiovascular function and circadian rhythms. This research also provides insights into the relationship between sleep cycles and other biological factors, helping unlock the potential for developing more effective therapies by considering variability in drug administration timing (Foster & Kritzman, 2004).

Paracetamol, or acetaminophen, is a commonly used drug as a fever reducer and pain reliever. Its mechanism of action is related to the inhibition of cyclooxygenase (COX) enzymes in the central nervous system, primarily in the brain. Although its mechanism of action is not fully understood, paracetamol provides antipyretic and analgesic effects without significant anti-inflammatory properties. It is generally recommended for managing mild to moderate fever and pain, such as headaches or muscle aches. The dosage of paracetamol varies depending on individual factors such as age and weight (Miller, C. D., & Brown, S. E., 2019). Paracetamol is usually administered orally in the form of tablets or syrup, although it can also be given through infusion in a hospital setting. The use of this

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drug should adhere to recommended dosage instructions and preferably be done under the supervision of a healthcare professional. Although considered safe at recommended doses, an overdose of paracetamol can cause serious liver damage (Brown, A., 2022). Attention to contraindications, potential drug interactions, and consultation with a healthcare professional before using paracetamol, especially in specific populations such as children or pregnant women, is necessary (Jones, M. A., & Smith, R. B., 2018).

COVID-19, caused by the SARS-CoV-2 virus, is a disease first identified in Wuhan, China, at the end of 2019. Its primary transmission occurs through respiratory droplets produced during coughing, sneezing, or talking. Symptoms vary from mild to severe, involving respiratory and general symptoms such as cough, shortness of breath, fever, fatigue, and loss of smell or taste. In terms of prevention, measures such as handwashing, mask usage, maintaining social distance, and avoiding crowds have been globally implemented. The World Health Organization declared COVID-19 a pandemic in March 2020, with widespread impacts on health, economic, and social sectors worldwide. Patient care involves isolation, supportive care, and sometimes intensive care, while vaccination and research continue to address this pandemic. The emergence of SARS-CoV-2 variants and psychological and social impacts are also focus areas of research and societal responses to the pandemic (Prasetyawan, F., 2023).

Through a chronopharmacological approach, this research will explore possible relationships between paracetamol administration at specific times and changes in patients' biological rhythms, particularly in the context of COVID-19 patients who may experience complex changes in their biological systems due to the infection (Miller, P., 2019). By further understanding how the timing of drug administration affects the body's response, this research is expected to open the door to increased treatment efficiency, reduced risk of side effects, and the development of more accurate and adaptive treatment guidelines for this unique patient population.

METHODS

This research has been structured using an analytical observational approach adopting a Cross-Sectional design and implementing a retrospective data collection method from the medical records of COVID-19 patients undergoing treatment at Dr. Soedomo Regional General Hospital in Trenggalek Regency during the year 2022. The primary focus of this study is to evaluate the effectiveness of paracetamol usage, a pharmacological agent commonly prescribed in the management of fever symptoms in COVID-19-infected patients.

The research population involves all inpatients diagnosed with COVID-19 who underwent paracetamol therapy during a specific time period. Sampling was conducted consecutively, with the inclusion of 100 patients to ensure representative results. Inclusion criteria were applied to ensure that patients diagnosed with COVID-19 and prescribed paracetamol at a dosage of every 8 hours per day were within the scope of this study. Several exclusion criteria were implemented to ensure the validity of the research, including patients receiving paracetamol less than 3 times a day. The main independent

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variable in this study is the time of paracetamol administration, divided into three different time intervals within a day, namely at 08:00 AM, 04:00 PM, and 10:00 PM. Meanwhile, the main dependent variable is the patient's body temperature response after undergoing paracetamol therapy, serving as the primary parameter for measuring treatment effectiveness.

Data analysis was conducted through the application of Chi-square statistical tests and T-dependent tests, aiming to gain a deep understanding of the comparison of paracetamol effectiveness in COVID-19 patients, considering the variability in administration timing. Statistical significance was set at a p-value of 0.05. This research is expected to provide additional insights into the clinical management of COVID-19, through further investigation into the effects of paracetamol administration timing, and to lay the foundation for the development of more targeted and personalized treatment strategies in response to the complexity of patient response variants to pharmacological therapy.

RESULTS AND DISCUSSION

This research involves a total of 100 patients as the study sample. The obtained data include the demographic distribution of patients, including age, gender, length of hospital stay, and the outcomes of COVID-19 patients admitted to and receiving paracetamol therapy at Dr. Soedomo Regional General Hospital in Trenggalek Regency in 2022.

Table 1. Patient Demographic

Karakteristik Responden	Data	
	Frequency	Percentage
Age		
<15 Years	8	8
16-35 Years	14	14
36- 50 Years	18	18
> 50 Years	60	60
Gender		
Male	74	74
Female	26	26
Legt of Stay		
<3 days	24	24
4-7 days	72	72
>7 days	4	4
Outcome		
Recovered	72	72
Deceased	28	28
Total	100	100

Table 1 displays the demographic data of 100 respondents who were subjects of the study. Observational results indicate the distribution of respondent characteristics across several categories, including age, gender, length of hospital stay, and treatment outcome.

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Regarding age, the majority of respondents are over 50 years old (60%), followed by the age group of 36-50 years with 18%. Overall, there is relatively even variation across all age groups. In terms of gender, the majority of respondents are male (74%), while females contribute about 26%.

When looking at the length of hospital stay, most respondents underwent treatment for 4-7 days (72%), with a significant percentage. Meanwhile, for hospital stays less than 3 days and more than 7 days, they contributed 24% and 4%, respectively. In terms of treatment outcomes, the majority of respondents recovered (72%), while around 28% experienced a deceased outcome.

The relatively balanced percentage across most demographic characteristics can be explained as a result of consecutive sampling. This process allows the inclusion of respondents with varying characteristics, creating a more representative picture of the population. However, it should be noted that these results may also be influenced by specific characteristics of the population under study or specific clinical settings affecting the distribution of respondent demographic characteristics. Further analysis is needed to understand the factors that may affect the results and the distribution of demographics in the study.

Table 2. Paracetamol Chronopharmacology

Temperature (°c)	ZT 08.00 WIB Mean		*p - value*	ZT 16.00 WIB Mean		*p - value*	ZT 22.00 WIB Mean		*p - value*
	Pre	*Post*		*Pre*	*Post*		*Pre*	*Post*	
36,5 -37,5	38,7	37,8	0,08	39,0	36,8	0,03	39,2	37,9	0,14

Source: Processed data, 2023

From the research results, we delve into the therapeutic effects on body temperature at three different times, namely zeitgeber 08:00 AM, zeitgeber 04:00 PM, and zeitgeber 10:00 PM. Data analysis shows changes in body temperature before (Pre) and after (Post) therapy, considering the mean values and their significance in p-values. It can be seen that at 08:00 AM (ZT 08:00), there is a decrease in the mean body temperature from 38.7°C to 37.8°C after therapy, although not statistically significant ($p = 0.08$). At 04:00 PM (ZT 04:00), a more significant decrease in body temperature is observed from 39.0°C to 36.8°C ($p = 0.03$). Meanwhile, at 10:00 PM (ZT 10:00), it is evident that despite a decrease in body temperature from 39.2°C to 37.9°C after therapy, this difference does not reach the expected level of significance ($p = 0.14$).

At 08:00 AM (ZT 08:00), it can be observed that therapy results in a decrease in the mean body temperature from 38.7°C (Pre) to 37.8°C (Post), although not statistically significant ($p = 0.08$). At this time, the natural variability in the body's rhythm or possibly a more limited body response to therapy may play a role in these results. It is important to remember that the human body has a circadian rhythm that can affect the response to treatment, and this needs to be considered in care management.

At 04:00 PM (ZT 04:00), a more significant decrease in body temperature is observed after therapy. The mean body temperature decreases from 39.0°C (Pre) to 36.8°C (Post)

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with a significant p-value (p = 0.03). This finding indicates that therapy at this time has a stronger impact on reducing body temperature, possibly because it is closer to the peak of the body's response to therapy.

At 10:00 PM (ZT 10:00), there is a decrease in body temperature from 39.2°C (Pre) to 37.9°C (Post), although this difference does not reach the expected level of significance (p = 0.14). Factors such as body rhythm variability and different body responses at this time may influence these results.

These findings highlight the importance of considering the administration time of therapy in body temperature management. At 04:00 PM, the body seems more responsive to therapy with a significant decrease in body temperature. This may be due to the body's circadian rhythm, which can influence the effectiveness of therapy at specific times. At 04:00 PM, the body reaches a specific point in its circadian cycle where its biological system may be more responsive to the therapeutic influence. Further understanding of circadian rhythms can help optimize the benefits of therapy and reduce potential side effects. Changes in gene expression, enzyme activity, and cellular receptor availability can vary during the circadian cycle, making the correct timing of therapy administration maximize its positive effects.

Limitations in this study include a relatively small sample size and individual variability in response to therapy. More research is needed to confirm and generalize these results. Nevertheless, these findings provide a basis for a deeper understanding of body responses to therapy at different times, paving the way for the development of more targeted and personalized treatment strategies. Individual variability in therapy response needs to be considered. These results may have clinical implications in determining the optimal time for administering therapy to achieve the desired effects.

This study, with its 100-patient sample, contributes valuable insights into the chronopharmacology of paracetamol and its impact on body temperature in COVID-19 patients. The observed variations in body temperature responses highlight the importance of timing in therapeutic interventions.

The results from this research underscore the significance of considering the circadian rhythm in clinical management. The body's natural biological clock influences its response to pharmacological interventions, and acknowledging this rhythmic variation can aid in tailoring treatment strategies. The observed temperature reductions post-therapy at different times suggest that the effectiveness of paracetamol may vary throughout the day.

The findings at 04:00 PM (ZT 04:00), indicating a more pronounced decrease in body temperature, are particularly noteworthy. This time coincides with potential peaks in metabolic activity or specific molecular processes that enhance therapy effectiveness. Understanding these circadian rhythms can guide healthcare professionals in optimizing treatment benefits and minimizing adverse effects.

Despite the notable insights gained, this study has its limitations, including the relatively small sample size and the need for further research to validate and generalize the results. Nevertheless, the groundwork laid by this research emphasizes the importance of

investigating the circadian aspects of drug efficacy, fostering the development of more sophisticated and personalized treatment approaches.

CONCLUSION

The findings illustrate the importance of considering the timing of therapy administration as a key factor in managing body temperature. At 4:00 PM (UTC+7), it is evident that the body exhibits a more significant response to the therapy, reflected in a substantial decrease in body temperature. This phenomenon can be explained by the presence of the body's circadian rhythm, a natural pattern influencing various physiological functions in the human body over a 24-hour period. The conclusion drawn from this research forms the foundation for emphasizing the concept of "right time, right dose" in clinical practice. Taking into account the body's circadian rhythm becomes essential in designing effective treatment protocols and personalizing care, aiming to ensure optimal outcomes. The results of this study can contribute significantly to the development of precise and time-oriented practical guidelines for therapy administration, thereby enhancing overall clinical effectiveness and response.

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