



Chronopharmacological Insights: Enhancing Acetaminophen Administration Timing for Inpatient COVID-19 Management

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Article Info	ABSTRACT
Corresponding Author: Fendy Prasetyawan E-mail: fendy.pra@gmail.com	The global COVID-19 pandemic has posed unprecedented challenges to global health. Dr. Soedomo Regional General Hospital in Trenggalek, which is involved in the management of COVID-19 patients, has witnessed a long journey in responding to and treating individuals infected with the SARS-CoV-2 virus. The use of acetaminophen has been a primary focus in efforts to improve standards of care and understanding symptom management in COVID-19 patients. Chronopharmacological analysis of acetaminophen use in COVID-19 patients at Dr. Soedomo Hospital aims to provide insight into how the timing of drug administration can affect therapeutic responses. There is evidence that the body's circadian rhythm can influence the metabolism and pharmacological effects of drugs, but this perspective has not been fully explored in the context of COVID-19. This study involved an analytical observational approach with a Cross-Sectional design and retrospective data collection method from the medical records of COVID-19 patients treated at Dr. Soedomo Regional Hospital in Trenggalek District. The results of the study showed that acetaminophen therapy at 16.00 WIB resulted in a more significant reduction in body temperature compared to other times. A deeper understanding of the body's circadian rhythm can help optimize the benefits of therapy and reduce potential side effects. Although there are limitations to this study, these results provide a basis for the development of more targeted and personalized treatment strategies. The clinical implications of this research can help in determining the optimal timing for administering therapy to achieve desired effects in COVID-19 patients. Keywords: Chronopharmacological, Acetaminophen, COVID-19

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INTRODUCTION

The global COVID-19 pandemic that has hit the entire world has created an unprecedented global health challenge. Regional General Hospital Dr. Soedomo in Trenggalek, as a health entity involved in treating COVID-19 patients, has witnessed a long journey in responding to and treating individuals infected with the SARS-CoV-2 virus (Prasetyawan, F., 2023). In an effort to continually improve standards of care and

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understanding of symptom management, the use of medications, such as acetaminophen, has become a major focus of attention (Smith, J., 2020).

The COVID-19 pandemic that has hit the world has exposed various complexities and challenges in the management of patients infected with the SARS-CoV-2 virus. Since the emergence of the COVID-19 pandemic, health services around the world have faced enormous challenges in responding to and treating patients infected with the SARS-CoV-2 virus. Dr. Hospital Soedomo in Trenggalek, as a health entity actively involved in treating COVID-19 patients, continues to strive to improve understanding and approaches in effective and safe patient management. In this context, the use of acetaminophen has become one of the main strategies for treating symptoms such as fever and pain in COVID-19 patients (Saristiana, Y., 2023).

Acetaminophen, or paracetamol, is a drug that is often used to relieve fever and reduce pain. However, its less focused use of time aspects in the context of chronopharmacology creates the potential to increase the effectiveness of treatment and provide a deeper understanding of how the body's biological rhythms can influence the response to drugs (Akhmal, F., 2024). Along with that, the current limited knowledge regarding how acetaminophen interacts with the body's circadian cycle, especially in COVID-19 patients, provides a strong basis for further research (Brown, A., 2021).

Chronopharmacological analysis of the use of acetaminophen in COVID-19 patients can provide in-depth insight into how the timing of drug administration can influence the body's response to treatment (Saristiana, Y., 2024). There is evidence that the body's circadian rhythm can influence the metabolism and pharmacological effects of a drug (Prasetyawan, F., 2024). There are differences in response to acetaminophen based on the time of administration, especially considering the variations in circadian rhythm that may occur in hospitalized COVID-19 patients. This analysis may pave the way toward increasing therapeutic efficacy, reducing side effects, and better understanding the pharmacologic dynamics of acetaminophen in this specific patient population. Although the use of acetaminophen is generally recognized, the chronopharmacological perspective, namely the study of the relationship between the timing of drug administration and the body's biological response, has not been fully explored. The body's circadian rhythm is known to influence the metabolic mechanisms and pharmacological response of a drug (Johnson, M., 2019).

Chronopharmacological analysis of the use of acetaminophen in COVID-19 patients at RSUD Dr. Soedomo Trenggalek aims to provide an in-depth understanding of how the timing of drug administration can influence the therapeutic response (Prasetyawan, F., 2024). Through this research, it is hoped that useful information can be found to guide clinical decisions regarding the use of acetaminophen, thereby increasing the effectiveness of treatment, reducing side effects, and detailing more personalized treatment guidelines (Anderson, R., 2022). By understanding in more detail the chronopharmacological aspects of COVID-19 patients, it is hoped that this can open the door to improving treatment strategies that are more careful and tailored to individual biological characteristics.

This study aims to analyze the chronopharmacology of acetaminophen use in COVID-19 patients at RSUD Dr. Soedomo Trenggalek, focusing on the body's biological response to drugs at various time points in a 24-hour cycle. With a deeper understanding of how the timing of acetaminophen administration affects the therapeutic effect and tolerability, it is

hoped that this research can provide a solid scientific basis for the development of more personalized treatment guidelines (Davis, S., 2021).

Through a chronopharmacology approach, this research will explore the possible relationship between administering acetaminophen at certain times and changes in the patient's biological rhythms, especially in the context of COVID-19 patients who may experience complex changes in their biological systems due to infection (Miller, P., 2019). By further understanding how the timing of drug administration influences the body's response, this research will hopefully open the door to increased treatment efficiency, reduced risk of side effects, and the establishment of more accurate and adaptive treatment guidelines for this unique patient population.

Literature Review

Research on chronopharmacology has become an important factor in understanding medication use, especially in the context of certain health conditions such as COVID-19 infection. Research related to chronopharmacological analysis of acetaminophen use in COVID-19 patients at Dr. Soedomo Trenggalek is a relevant research topic to explore more deeply the impact of biological time on drug effectiveness and tolerability.

Research has shown that circadian rhythms play a significant role in the body's immune response to infection. Given that COVID-19 has systemic impacts involving the immune response, chronopharmacological studies on acetaminophen use may provide insight into how the timing of drug administration influences the reduction of fever and other symptoms in COVID-19 patients. Previous studies have also highlighted the role of circadian rhythms in drug pharmacokinetics, and this analysis may provide a basis for optimal dose adjustment of acetaminophen at various times in COVID-19 patients.

Chronopharmacology

Chronopharmacology is a field of study that explores how drug effects may change over biological time and the body's endogenous cycles. Biological functions, including cardiovascular functions such as the heart and blood vessels, show circadian rhythms that reflect changes in activity within a 24-hour period (Wilson, C., 2018). Epidemiological studies have shown 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 repeating 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, changes in body temperature follow a certain pattern, reaching a peak in the afternoon, then decreasing gradually as night falls, and dropping drastically during sleep (White, L., 2020). Understanding chronopharmacology allows us to better understand how biological timing influences the body's response to drugs, especially in the context of cardiovascular function and circadian rhythms. This research also provides insight into the relationship between sleep cycles and other biological factors, helping to unlock the potential for developing more effective therapies that take into account variability in timing of drug administration (Foster & Kritzman, 2004).

Acetaminophen

Acetaminophen, or paracetamol, is a drug that is often used to reduce fever and relieve pain. The mechanism of action is related to the inhibition of the cyclooxygenase (COX) enzyme in the central nervous system, especially in the brain. Although its mechanism of action is not completely understood, acetaminophen provides antipyretic and

analgesic effects without significant anti-inflammatory properties. This drug is generally recommended for treating fever and mild to moderate pain, such as headaches or muscle aches. Acetaminophen dosage varies depending on individual factors such as age and body weight (Miller, CD, & Brown, SE, 2019).

Acetaminophen is usually given orally in tablet or syrup form, although it can also be given intravenously in a hospital setting. Use of this drug must be in accordance with the recommended dosage instructions and should be done under the supervision of a health professional (Brown, A., 2022). Although considered safe at recommended doses, acetaminophen overdose can cause serious liver damage. It is important to pay attention to contraindications and potential drug interactions, and consult a health professional before using acetaminophen, especially in special populations such as children or pregnant women (Jones, MA, & Smith, RB, 2018).

COVID-19

COVID-19, which is caused by the SARS-CoV-2 virus, is a disease that was first identified in Wuhan City, China at the end of 2019. Transmission occurs mainly through respiratory droplets produced when coughing, sneezing or talking. Symptoms range from mild to severe, involving respiratory and general symptoms such as coughing, shortness of breath, fever, fatigue, and loss of sense of smell or taste. In the context of prevention, measures such as washing hands, wearing masks, maintaining social distance, and avoiding crowds have been implemented globally. WHO 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 vaccinations and research continue to address the pandemic. The emergence of the SARS-CoV-2 variant and its psychological and social impacts have also become the focus of research and society's response to the pandemic (Prasetyawan, F., 2023)

METHODS

This research was designed using an analytical observational approach with a cross sectional design and applied a retrospective data collection method from the medical records of COVID-19 patients treated at RSUD dr. Soedomo Trenggalek Regency in 2022. The main focus of the research is to evaluate the effectiveness of using the drug acetaminophen, which is generally prescribed to manage symptoms such as fever in COVID-19 patients.

The study population included all inpatients diagnosed with COVID-19 and receiving acetaminophen therapy during the specified time period. Sampling was carried out consecutively, and a total of 100 patients were included in this study to achieve representative results. Inclusion criteria ensured that patients diagnosed with COVID-19 were prescribed acetaminophen doses every 8 hours a day. A number of exclusion criteria were implemented to ensure the validity of the study. Patients prescribed acetaminophen less than 3 times daily were not included in this study. The main independent variable is the time of administration of acetaminophen, which is divided into three different time intervals in a day, namely 08.00 WIB, 16.00 WIB, and 22.00 WIB. Meanwhile, the main dependent variable is the patient's body temperature response after undergoing acetaminophen therapy, which is the main parameter for measuring the effectiveness of treatment.

Data analysis was carried out by applying the Chi-square statistical test and T-dependent test to gain an in-depth understanding of the comparative effectiveness of acetaminophen in COVID-19 patients, taking into account the variability in administration time with a p-value of 0.05.

RESULTS AND DISCUSSION

In this study, there were 100 patients who were the research samples. The data obtained includes the demographic distribution of patients including age, gender, length of stay and outcomes of COVID-19 patients who were hospitalized and received Acetaminophen therapy at RSUD dr. Soedomo Trenggalek Regency in 2022.

Table 1. Patient Demographic Data

Respondent Characteristics	Amount	
	Frequency	Percentage (%)
Age		
<15 Years	8	8
16-35 Years	14	14
36- 50 Years	18	18
> 50 Years	60	60
Gender		
Man	74	74
Woman	26	26
Length of Hospitalization		
<3 days	24	24
4-7 days	72	72
>7 days	4	4
Outcomes		
Healed	72	72
Die	28	28
Total	100	100

Table 1 shows that there is demographic data from the 100 respondents who were research subjects. The observation results show the distribution of respondents' characteristics in several categories, including age, gender, length of stay, and treatment outcomes. In terms of age, the majority of respondents were over 50 years old (60%), while the 36-50 year age group followed with 18%. Overall, there was fairly even variation across age groups. Regarding gender, the majority of respondents were men (74%), while women accounted for around 26%. When looking at the length of stay, most respondents experienced treatment for 4-7 days (72%), a significant percentage. Meanwhile, length of stay of less than 3 days or more than 7 days contributed 24% and 4% respectively. In terms of treatment outcomes, the majority of respondents managed to recover (72%), while around 28% experienced the outcome of death.

The relatively balanced percentages for most of these demographic characteristics can be explained as the result of a consecutive sampling process. This process allows for

the inclusion of respondents who vary in their 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 that is the focus of the study or specific clinical settings that influence the distribution of respondents' demographic characteristics. Further analysis is needed to better understand the factors that may influence the results and demographic distribution of the study.

Table 2. Chronopharmacology of Acetaminophen

Body temperature (°c)	ZT 08.00 WIB		p - value	ZT 16.00 WIB		p - value	ZT 22.00 WIB		P - value
	Mean Pre	Mean Post		Mean Pre	Mean Post		Mean Pre	Mean 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 results of the research, we explored the impact of therapy on body temperature at three different times, namely Zeitgeber 08.00, Zeitgeber 16.00, and Zeitgeber 22.00. Data analysis shows changes in body temperature before (Pre) and after (Post) therapy by paying attention to the mean value and its significance in the p value, it can be seen that at 08.00 WIB (ZT 08.00), there was a decrease in the average body temperature from 38.7°C to 37.8°C after therapy, but not significant ($p = 0.08$). At 16.00 WIB (ZT 16.00), body temperature decreased more significantly from 39.0°C to 36.8°C ($p = 0.03$). Meanwhile, at 22.00 WIB (ZT 22.00), it was seen that although there was a decrease in body temperature from 39.2°C to 37.9°C after therapy, this difference did not reach the expected level of significance ($p = 0.14$).

At 08.00 WIB (ZT 08.00), it was seen that therapy resulted in a decrease in average body temperature from 38.7°C (Pre) to 37.8°C (Post), although it was not statistically significant ($p = 0.08$). At this time, natural variability in body rhythms or perhaps 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 influence response to treatment, and this needs to be considered in treatment management.

At 16.00 WIB (ZT 16.00), there was a more significant reduction in body temperature after therapy. Mean body temperature decreased from 39.0°C (Pre) to 36.8°C (Post) with a significant p value ($p = 0.03$). These findings indicate that therapy at this time has a stronger impact on reducing body temperature, perhaps because it is closer to the peak of the body's response to therapy.

At 22.00 WIB (ZT 22.00), there was a decrease in body temperature from 39.2°C (Pre) to 37.9°C (Post), although this difference did not reach the expected level of significance ($p = 0.14$). Factors such as variability in body rhythms and different body responses at these times may influence these results.

These findings highlight the importance of considering the timing of therapy administration in the management of body temperature. At 16.00 WIB, the body appeared more responsive to therapy with a significant decrease in body temperature. This can be caused by the body's circadian rhythm which can affect the effectiveness of therapy at certain times. At 16.00 WIB, the body looked more relaxed. This shows that managing the timing of therapy can be a critical factor in achieving the desired effect.

This circadian rhythm is influenced by hormonal and molecular regulations that control various biological processes, including the response to certain drugs or therapies

(Garcia, F., 2021). At 16.00 WIB, the body reaches a certain point in its circadian cycle where its biological systems may be more responsive to the influence of therapy. This could be related to peaks in metabolic activity or certain molecular activities that support the effectiveness of therapy at that time. Further understanding of circadian rhythms may help in optimizing therapeutic benefits and reducing potential side effects. Changes in gene expression, enzyme activity, and cellular receptor availability may vary during the circadian cycle, so appropriate timing of therapy administration can maximize its positive effects.

Limitations in this study include the relatively small sample size and individual variability in response to therapy. More research is needed to confirm and generalize these results. Nonetheless, these results provide a basis for further understanding of the body's response patterns to therapy over time, which may pave the way for the development of more targeted and personalized treatment strategies. Individual variability in response to therapy needs to be considered. These results may have clinical implications in determining the optimal timing for administration of therapy to achieve the desired effect. By understanding the body's response patterns to therapy at different times, the development of more targeted and personalized treatment strategies can be pursued.

CONCLUSION

This research was conducted involving 100 COVID-19 patients who received Acetaminophen therapy at RSUD dr. Soedomo Trenggalek Regency in 2022. Patient demographic data shows a fairly even distribution in several categories, including age, gender, length of stay and treatment outcomes. The majority of respondents were over 50 years old, with the majority being male and most experiencing hospitalization for 4-7 days. Most respondents managed to recover from COVID-19, while around 28% experienced the outcome of death. Chronopharmacological analysis of Acetaminophen showed significant differences in the reduction of patient body temperature after therapy at different times. At 16.00 WIB, therapy showed a significant reduction in body temperature, while at 08.00 WIB and 22.00 WIB, the difference was not significant. These findings highlight the importance of considering the timing of therapy administration in achieving the desired effect, given that the body's response to therapy can vary depending on circadian rhythms.

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