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by Farah Hendara

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THE EFFECT OF PARACETAMOL AND CODEINE ANALGESIC COMBINATION ON SERUM GLUTAMIC OXALOACETATE TRANSAMINASE LEVELS IN MALE WISTAR RATS

Rona Ayu Hanifah [1], Farah Hendara Ningrum [2], Erwin Kresnoadi [3] , Satrio Adi Wicaksono [3]
[1]Undergraduate Student, Faculty of Medicine, Diponegoro University
[2]Departement of Radiology, Faculty of Medicine, Diponegoro University
[3]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Diponegoro University
*Corresponding email = satriowicaksono@fk.undip.ac.id

ABSTRACT

Introduction : Paracetamol is an effective analgesic to relieve mild to moderate pain when it is used in therapeutic doses. Codeine is an opioid analgesic to relieve moderate to severe pain. Both are metabolized in the liver and have different mechanisms in the treatment of pain. The use of paracetamol and codeine as monotherapy has been extensive, but research on the effectiveness of these drugs in combination is still limited, especially about its effect in liver damage. This study was to investigate the effect of paracetamol and codeine analgesic combination Serum Glutamic Oxaloacetate Transaminase levels in male Wistar rats. **Method :** This was an experimental study using Post-Test Only Control Group Design. The samples were 24 male wistar rats randomized into 4 groups; group I (control group, without treatment), group II receiving paracetamol 32 mg/kgBB, group III receiving codeine 1,9 mg/kgBB, and group IV receiving combination of paracetamol 32 mg/kgBB and codeine 1,9 mg/kgBB. Drugs were administered through oral gastric instillation 4 times a day for 28 days. Blood samples were collected at the 29th day through retroorbital vessel to measure the SGOT levels. The data was analysed using One-Way ANOVA test and Post-Hoc test. **Results** : The results of this research were obtained from statistical tests where there was no significant increase of the levels of Serum Glutamic Oxaloacetate Transaminase of Wistar rats which received a combination of paracetamol and codeine in the control group (p = 0.005). While in the other group there was not significant differences of the levels of Serum Glutamic Oxaloacetate Transaminase. **Conclusion** : There is no significant difference of Serum Glutamic Oxaloacetate Transaminase levels between the administration of paracetamol and codeine combination compared to the control group.

Keywords : Paracetamol, codeine, paracetamol and codeine combination, SGOT levels, pain

INTRODUCTION

Pain is a symptom that is often complained by patients and the reason for his arrival to the health service. Globally, an estimated 1 in 5 adults experience pain and 1 in 10 adults is diagnosed with chronic pain each year. Pain is experienced by all populations in the world, regardless of age, gender, income, race or geography. Pain is not evenly distributed throughout the world. [1]

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience that is associated with actual tissue damage and potential tissue damage. Prevention and treatment of pain is an important aspect of health care.[2]

Category of pain is based on pain with impaired function in cancer patients. The pain scale is calculated with a numerical scale of 0-10 based on pain disorders with function, a scale of 0 indicates no pain, a pain scale 1-4 indicates moderate pain, a scale of 5-6 indicates moderate pain, and a scale of 7-10 indicates severe pain.[3]

Based on the Adaptation of Analgesic Ladder of the World Health Organization, management of pain can be distinguished by its intensity. In pain with mild intensity can use paracetamol or NSAID or NSAID combination with adjuvant analgesics.

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Moderate intensity pain can be treated with NSAIDs or a combination of NSAIDs with adjuvant analgesics or a combination of NSAIDs and adjuvant analgesics with weak opioids. Severe intensity pain can be treated with NSAIDs, strong opioids, a combination of NSAIDs with strong opioids, or a combination of NSAIDs and strong opioids with adjuvant analgesics.[4]

Analgesics are drugs that are used to relieve pain. Analgesic drugs are divided into two groups, namely opioid drugs and NSAIDs. Opioids work on the central nervous system, while NSAIDs work on the peripheral nerve receptors and the central nervous system. [5]

Multimodal analgesia is the use of more than one type of analgesic that has different mechanisms to get addictive and synergistic effects. Opioid analgesics are systemic analgesia for the treatment of moderate to moderate pain, for example opioid analgesics include morphine, codeine, tebain, and pepain. Based on research by White PF et al in 2010 stated that there are 12 regimens that can be combined with opioid analgesics, namely paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase inhibitors, alpha 2 agonists, ketamine, gabapentin and pregabalin.[6]

Paracetamol or acetaminophen is an antipyretic analgesic drug that is very popular in the community and is used as a pain reliever from mild to moderate pain.[7] Paracetamol works by inhibiting weak prostaglandins in tissues.[8] Paracetamol has proven analgesic and antipyretic effects, but its anti-inflammatory effect is very weak and has a very weak and anti-inflammatory effect. began widely used as an acute pain reliever after surgery.[9]

Codeine is an opoid analgesic that is indicated to relieve mild to moderate pain.[10] The analgesic effect of codeine works predominantly through its metabolism to morphine through the CYP2D6 enzyme. [11]

The combination of paracetamol and opioids is an attractive choice, especially for individuals who have a history of NSAID contraindications. Paracetamol and codeine have better analgesic effects compared to single-dose paracetamol, and do not provide serious side effects.[9]

The liver is the most active tissue for metabolizing drugs. Metabolism of drugs in the liver can cause damage to the liver cells themselves. In the United States, around 2000 cases of acute liver disease occur each year and more than 50% are caused by drugs (37% are due to acetaminophen, 13% are idiosyncratic reactions to other drugs). Acetaminophen or paracetamol is the main cause of drug induced toxic injury in several organ systems, including the liver as part of the gastrointestinal tract.

Liver cell abnormalities can be seen based on the measurement of the activity levels of the enzymes Serum Glutamate Oxaloacetate Transaminase (SGOT) and Serum Glutamate Pyruvate Transaminase (SGPT). Increased levels of the SGOT and SGPT enzymes indicate damage to the liver cell wall, so that the enzyme can be used as a marker of impaired liver cell integrity (hepatocellular).

From the background of these problems, researchers want to conduct research on the effect of administering analgesic combinations of paracetamol and codeine on SGOT levels in which research on the side effects of these combinations on liver function is still limited.

RESEARCH METHODS

Sample and Treatment

The research was experimental with Post Control Only Control Group Design approach using 20 male wistar rats as research object. Treatment was performed for 28 days. The experimental animals were divided into 4 groups: control and treatment groups (Table 1) in which each group was 5

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animals with the following criteria:
a. Inclusion criteria:
(1) Male wistar rat,
(2) Age 2-3 months,
(3) Healthy and active,
(4) Weight 200-250 grams,
(5) No anatomical abnormalities.
b. Exclusion criteria: Mice died during adaptation and treatment.

Table 1. Classification of control groups and treatment groups

Group	Treatment
K	Control group fed standard foods and drinks
P1	Rats fed standard foods and drinks + paracetamol 32 mg/kgBB 4 times daily for 28 days
P2	Rats fed standard foods and drinks + codeine 1,9 mg/kgBB 4 times daily for 28 days
P3	Rats fed standard food and drinks + combination of paracetamol 32 mg/kgBB and codeine 1,9 mg/kgBB 4 times daily for 28 days

The doses of paracetamol and codeine used are the result of conversion from human dose to mouse dose. Paracetamol dose calculation was 500 mg x 0,018 x (50 kg : 70 kg) : 200 gram = 32 mg/kgBB, dose of codeine 30 mg x 0,018 x (50 kg : 70kg) : 200gram = 1,9 mg/kgBB, and combination of paracetamol dose 500 mg x 0,018 x (50 kg : 70 kg) : 200 gram = 32 mg/kgBB and codeine 30 mg x 0,018 x (50 kg : 70kg) : 200gram = 1,9 mg/kgBB.

Before being treated, all of the wistar rats were acclimatized beforehand and fed the same standard of drinking and drinking for 1 week ad libitum. After that, each group of wistar rats was given treatment in accordance with the previously mentioned for 28 days. Furthermore, wistar rats were drawn blood through a retroorbita blood vessel on day 29. It then measured the levels of SGOT in the Clinical Pathology laboratory.

Measurement of SGOT Levels

Blood samples taken directly from retroorbita blood vessels, then examined levels of SGOT with IFCC Without Pyridoxal Phosphate 37^{o}C examination method. The unit used is IU / L.

Data analysis

The data obtained were processed by computer program and analyzed by normality test of Saphiro-Wilk, Levene homogenity test, and One Way ANOVA statistic test. Post-Hoc test as a further difference test was done to see the difference in each group and said to be significant when $p < 0.05$.

RESEARCH RESULT

Serum Glutamic Oxaloacetic Transaminase (SGOT) levels

The obtained data from the examination of serum glutamic oxaloacetic transaminase levels are numerical data. Serum glutamic pyruvate transaminase levels were measured by automatic analyzer in units of mg/dl. Descriptive analysis of serum glutamic oxaloacetic transaminase levels can be seen in the following table.

Table 2. Desciptive Analysis

Group	Mean	Standart deviation
Control	123.91	24.987
Treatment 1	97.46	19.75
Treatment 2	95.71	20.67
Treatment 3	97.51	18.54

Based on table 2, the highest mean of the serum glutamic oxaloacetic transaminase level was in the control group (123,91), while the lowest mean was in the treatment group 2 (95,71). The obtained data were tested for normality using the Saphiro-Wilk test. The results can be seen in table 3.

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Table 3. Test normality and homogeneity

Group	Saphiro-Wilk Sig.	Levene Sig.
Control	0.294	0. 917
Treatment 1	0.101	
Treatment 2	0.131	
Treatment 3	0.759	

From the table above, there is normal data distribution (p> 0.05) also homogeneous data variations (p> 0.05). Because of that, we continue the test using the One Way ANOVA test. Comparative test results can be seen in table 4.

Table 4. *One Way ANOVA test*

Groups	P
Control	0.147
Treatment 1	
Treatment 2	
Treatment 3	

*significant p<0.05

From the table above, the value of p> 0.05; that means the data is not significant.

DISCUSSION

The aim of this study was to determine the SGOT levels of wistar rats on oral administration of paracetamol and codeine analgesic. The sample of this study was 20 male Wistar rats based on predetermined inclusion criteria. The sample was divided into 4 groups, namely the control group, the first treatment group with 32 mg / kgBB of paracetamol given orally 4 times a day, the second treatment group by giving codeine 1.9 mg / kgBB orally 4 times a day, and the third treatment group by giving a combination paracetamol dose 32 mg / kg body weight and codeine 1.9 mg / kg body weight orally 4 times a day in which each group consisted of 5 wistar rats.

In the first treatment group, administration of paracetamol at a dose of 32 mg / kgBB orally 4 times a day there was no significant difference in SGOT levels. There are several factors that can influence the results of research. The dose used can be one of the factors that can affect the results of this study, in this study using a paracetamol dose of 32 mg / kg or the equivalent of 500 mg in humans. Paracetamol is a drug that is often used to relieve pain and has a good safety profile. At high doses, paracetamol can cause severe hepatic necrosis and fatal liver failure.[29] In previous studies, the use of paracetamol at a dose of 250 mg / kgBB orally once can cause congestion, degeneration, and focal hepatic lobular necrosis after 48 hours of administration.

Hepatotoxicity from paracetamol occurs through the formation of excessive amounts of dangerous NAPQI metabolites. However, if NAPQI is present in toxic doses, glutathione cannot completely detoxify and NAPQI will react with liver protein and covalent binding occurs with liver macromolecules, then liver necrosis occurs.[31]

In the second treatment group, wistar rats coded at a dose of 1.9 mg / kg orally 4 times daily for 28 days did not result in a significant increase in SGOT levels. Codeine is a weak opioid drug used as a moderate to severe pain therapy. The results found no significant difference in SGOT levels. This can be influenced by several factors, one of which is the administration dose of 1.9 mg / kgBW. In previous studies, the gradual administration of normal (5 mg / kgBB), high (25 mg / kgBB), and extreme (50 mg / kgBB) doses of codeine significantly increased SGOT levels in male wistar rats.[32]

Codeine hepatotoxicity is caused by codeine intermediates produced by cytochrome P-450, while monookoxygenase containing FAD can metabolize codeine into non-toxic intermediates.[27] Chronic administration of mice decreases the ability

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of liver fractions containing microsomes and dissolved proteins to demethylate morphine to formaldehyde.[33]

In the third treatment group, rats with paracetamol dose 32 mg / kgBB and codeine 1.9 mg / kgBB orally 4 times a day for 28 days there were no significant changes in SGOT levels. The dose factor can affect the results of the study. Until now there has been no research that measures the effect of giving a combination of paracetamol and codeine on SGOT levels. However, the combination of paracetamol dose of 500 mg and codeine dose of 30 mg can still provide effective analgesic effects and the occurrence of side effects is not significant.

In the data from this study it can be seen that the levels of SGOT in the combination analgesic group did not have a significant difference compared to the control group. In addition, in the group giving paracetamol and the group giving codeine also found no significant difference in SGOT levels compared with the control group. Then it can be concluded that the administration of a combination of paracetamol analgesics with a dose of 32 mg / kgBB and codeine dose of 1.9 mg / kgBB orally 4 times a day for 28 days did not cause significant hepatic impairment.

Therefore, further investigation is needed for this study. Limitations in this study are that researchers can not control some external factors such as environmental factors and other diseases, as well as internal mouse factors such as a history of rat disease, resistance, and stress levels each mouse. The limited time of study also became one of the limitations of researchers so that researchers can not make variations in research time.

CONCLUSIONS AND SUGGESTIONS

Conclusion

In this study it can be concluded that analgesic combination of paracetamol dosage of 32 mg/kgBB and codeine dose in amount 1,9 mg/kgBB 4 times daily for 28 days on serum glutamate oxaloatetate transaminase (SGOT) levels wistar mice did not cause a significant changes of SGOT levels.

Suggestions

It should be considered regarding the use of doses in analgesic combinations of paracetamol and codeine. Further research on the effect of analgesic combination of paracetamol and codeine on levels of SGOT on varying doses and durations, and on histopathologic images of the liver. In addition, further studies may be performed using other blood chemistry analyzes, and an epidemiological study of the safe dose of paracetamol and codeine in use as an analgesic drug should be performed.

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