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THE EFFECT OF ANALGESICS COMBINATION OF PARACETAMOL AND CODEINE ADMINISTRATION TO SERUM UREA IN MALE WISTAR RATS

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ABSTRACT

Background: A combination of the analgesic drug Paracetamol and Codeine can be used in moderate to severe pain management. Both are classified into two different groups of analgesics, thus they have a different mechanism of action. The combination of Paracetamol and Codeine provides better potential and work synergistically in pain management. This combination of analgesic drugs also has no potential side effects on the kidneys. **Objective:** To determine the combination of paracetamol and codeine analgesics on serum urea levels in male Wistar rats. **Method**: This study is an experimental study with a Post Test Only Control Group Design. Samples were 20 Wistar rats with certain criteria, randomly divided into 4 groups: control group, 32 mg/kgBW paracetamol group, 1,9 mg/kgBW codeine group, and 32 mg/kgBW paracetamol combination group and codeine 1,9 mg/kgBW. Giving is done orally with gastric sonde 4 times a day for 28 days. Day 29, blood is drawn through retroorbital vessels to measure serum urea levels. Statistical tests using the ANOVA and Post-Hoc tests. **Results:** The results obtained by the control group (32.1880), treatment group 1 (32.4240), treatment group 2 (32.3000), and treatment group 3 (31.1560). The One Way ANOVA statistical test results showed that the value of p = 0.970 (p> 0.05) which means there are no significant differences in serum urea levels between the four groups. **Conclusion:** There was no significant difference in the increase in the urea level between the combination of paracetamol and codeine compared to the control group. **Keywords:** Paracetamol, Codeine, Serum Ureum, Pain

INTRODUCTION

Until now, pain is one of the main complaints that most bring patients in and out of health care facilities. An estimated 6.6 million people from around the world die from cancer each year. Pain often occurs during cancer. Many cancer sufferers visit health services because of the pain they feel.[1] Pain is an unpleasant sensory and emotional experience due to tissue damage, both actual and potential, or as described in the form of the damage.[2]

Analgesics are a level of drugs that relieve pain without causing loss of consciousness.[3] Paracetamol is one of the most commonly used analgesics as an antipyretic drug and is included in non-narcotic analgesics available without a prescription, both in mono and multi-component preparations.[4] Codeine is an antitussive drug and analgesics that have been used since the 1800s. This drug is a mild class of opioids that are commonly used in pediatric patients, although research on the safety of using codeine in pediatric patients is still small.[5]

Excessive use of analgesic treatment can interfere with kidney function.[6] Parameters that can be used to determine kidney function are by examining urea levels in blood or serum, glomerular filtration rate, serum creatinine levels, urea clearance, and creatinine clearance. helps to establish a diagnosis of acute kidney failure. Measurement of serum urea can be used to evaluate kidney function, hydration status, assess nitrogen balance, assess the

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progression of kidney disease and assess hemodialysis results.[7]

From the background of the above problems, the researcher wants to research the effect of giving the analgesic combination of paracetamol and codeine on serum urea levels where research on the nephrotoxicity of this drug combination is still limited.

RESEARCH METHODS

Samples and Handling

This study uses an experimental form of research with a Post-Test Only Control Group Design approach that uses 20 male Wistar rats as research objects. The treatment was given for 28 days. Experimental animals were divided into 4 groups namely control and treatment groups (Table 1) where each group consisted of 5 experimental animals with criteria:

a. Inclusion criteria: (1) Male Wistar rats, (2) 2-3 months old, (3) Healthy and active, (4) Weight 200-250 grams, (5) No anatomical abnormalities.

b. Exclusion criteria: Mice die during adaptation and treatment.

Table 1. Control group and treatment group classified

Group	Treatment
K	The control group was given standard food and drink
P1	Rats were given standard food and drinks + paracetamol dose of 32 mg/kgBW 4 times a day for 28 days
P2	Rats were given standard food and drinks + codeine 1.9 mg/kgBW 4 times daily for 28 days
P3	Rats given standard food and drinks + combination of paracetamol dose of 32 mg/kgBW and codeine1.9mg /kgBW 4 times a day for 28 days

Based on the table, the dose conversion from humans to mice is 0.018. Calculation of the dose for the first treatment group given paracetamol is 500 mg x (50 kg: 70 kg) x 0.018: 200 gr = 32 mg/kgBW. The dose for the second treatment group that was given codeine was 30 mg x 50 kg: 70 kg x 0.018: 200 gr = 1.9 mg/kgBW. While the third treatment group was given a combination of paracetamol dose 500 mg x (50 kg: 70 kg) x 0.018: 200 gr = 32 mg/kgBW and codeine 30 mg x 50 kg: 70 kg x 0.018: 200 gr = 1.9 mg/kgBW. Dosing is done for 28 days.

Before being treated, all Wistar rats were acclimatized by being staged and fed the same standard and drink for 1-week ad libitum. After that, each group of Wistar rats was treated according to those previously mentioned for 28 days. Furthermore, Wistar rats were taken blood through retroorbital blood vessels on day 29. Then measured serum urea levels in the Clinical Pathology laboratory.

Urea Level Measurement

Blood samples are taken directly from retroorbital vessels, then an examination of Ureum levels using the Jaffe examination method without deproteination. The unit used is Mg/dl.

Data analysis

The data obtained were processed using a computer program and analyzed with the Shapiro-Wilk normality test, the Levene homogeneity test, and the One Way ANOVA statistical test. Post-Hoc Test as a follow-up test was carried out to see the differences in each group and was said to be significant if $p < 0.05$.

RESEARCH RESULT

Urea content

The highest mean urea level was found in treatment group 1 (32.4240), while the lowest was in treatment group 3 (31.1560) (Table 2). Data are normally distributed (Table 3). The One Way

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ANOVA statistical test results showed that the value of p = 0.970 (p> 0.05) which means there are no significant differences in serum urea levels between the four groups.

Table 2. Creatinine levels in the control group and the treatment group

Group	Mean	Standard Deviation
Control	32,1880	3,86124
Treatment 1	32,4240	2,47547
Treatment 2	32,3000	5,77966
Treatment 3	31,1560	5,42680

Table 3. Normality and Homogeneity Test

Group	Shapiro-Wilk	Levene
	Sig.	**Sig.**
Control	0,669	
Treatment 1	0,336	0,306
Treatment 2	0,073	
Treatment 3	0,218	

Tabel 4. *One Way ANOVA* test

Group	P
Control	0,970
Treatment 1	
Treatment 2	
Treatment 3	

*Significant p<0.05

DISCUSSION

The sample of this study was 20 male Wistar rats that met the specified inclusion criteria. The rats were acclimatized for 7 days. After acclimatizing the 20 rats were divided into 4 groups. The first group was 5 male Wistar rats as a control group (feeding standard Wistar rats). The second group was 5 male Wistar rats as the first treatment group (administration of a dose of 32 mg / kgBW paracetamol orally 4 times a day for 28 days). The third group was 5 male Wistar rats as the second treatment group (administration of codeine dose of 1.9 mg/kgBW mg orally 4 times a day for 28 days). The fourth group was 5 male Wistar rats as the third treatment group (giving a combination of codeine dose of 1.9 mg/kgBW mg and paracetamol dose 32 mg/kgBW orally 4 times a day for 28 days).

In the first treatment group, the administration of paracetamol at a dose of 32 mg/kgBW did not cause significant changes in urea levels. This can be seen in the average paracetamol group where the average urea level is 32.42 mg/dl.

This is consistent with previous research showing that an overdose of paracetamol can lead to kidney dysfunction, but the use of recommended therapeutic doses is relatively safe with low side effects.[8] Even so, paracetamol at therapeutic doses can be dangerous if given to patients consuming alcohol or drugs that stimulate excessive P450 microsomal oxidase enzymes.[9] While in use with excessive doses, it will cause toxic and cause damage to organs in the body, one of which is the kidneys. The mechanism of paracetamol toxicity occurs due to the conversion of the drug into a very active, electrophilic, and toxic metabolite for the liver and kidneys, namely N-acetyl-benzoquinone imine (NAPQI) by the cytochrome P450 enzyme. NAPQI causes tubular damage which is marked by increased levels of serum creatinine and urea which can ultimately lead to kidney failure.[10]

Another factor that can affect is the duration of drug administration. In this study, the duration of drug administration was only 28 days. Based on Cynthia A. Naughton's study, the use of paracetamol at a dose of more than 1 gram per day for 2 years increases the risk of chronic interstitial nephropathy.[11]

In the second treatment group, it was found that the administration of codeine

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dose of 1.9 mg/kgBW did not cause significant changes in urea levels. This can be seen in the average codeine group where the average urea level is 32.3 mg/dl.

In this study, the results showed there was no increase in serum urea levels. This can be influenced by several factors, one of which is the administration dose of 1.9 mg/kgBW. Based on Abiodun Olusoji Owoade's research, administration of high-dose codeine (25 mg/kgBW) and extreme doses (50mg/kgBW) for 28 days caused a significant increase in serum urea levels of male Wistar rats.[12]

Codeine, like other opiate receptor agonists commonly used clinically, works through activation of the μ receptor (Mu Opioid Receptor, MOR). MOR is present in the CNS, neural networks other than the CNS, and non-neuronal tissues.[13-15] The presence of extensive MOR in various tissues makes the use of codeine very susceptible to side effects associated with opiate compounds. Side effects related to the use of codeine mediated by MOR include respiratory depression due to decreased sensitivity of carbon dioxide chemoreceptors in the medulla, nausea, and vomiting due to stimulation of the vomiting center in the medulla.[16-17] So it does not cause a significant increase in serum urea levels.

In the third treatment group, the results obtained on the combination of paracetamol 32 mg/kgBW and codeine dose of 1.9 mg/kgBW did not cause significant changes in urea levels compared with the control group. This can be seen in the average combination group of paracetamol and codeine where the average urea level is 31.15 mg/dl.

The dosage factor can affect the results of the study. Until now there has been no research that measures the effect of providing a combination of paracetamol and codeine on serum creatinine levels. However, the combination of paracetamol at a dose of 500 mg and codeine at a dose of 30 mg can still provide an effective analgesic effect and the occurrence of insignificant side effects.[18] The administration of a combination of paracetamol at a dose of 650 mg and codeine at a dose of 60 mg increases the side effects of the drug.[19]

From the data of this research, it can be seen that the mean serum urea level in all treatment groups did not increase significantly.

In this study, there are limitations that the author cannot control several external factors, including the environment, treatment and nutritional intake, and rat internal factors such as stress and endurance of mice.

CONCLUSIONS AND SUGGESTIONS

In this study, it can be concluded that the administration of a combination of analgesic drug paracetamol dose 32 mg/kgBW and codeine dose of 1.9 mg/kgBW 3 times a day for 28 days orally caused a significant difference in serum urea levels.

Further research needs to be done on the effect of providing a combination of paracetamol and codeine using varying dosages and duration of exposure, as well as supplementing with renal histopathology test. After that, epidemiological studies on safe doses of a combination of paracetamol and codeine are also needed as analgesic options are needed.

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