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Detection of Acute Toluene Exposure to Increase Value Malondialdehyde (MDA) and Increase in Number of Lipid Vacuoles Male Wistar Rat Myocardium

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Abstract

Background: Exposure to toluene perihalasi can cause oxidative stress in the myocardium through the formation of Reactive Oxygen Species (ROS) which will trigger oxidative stress with the formation of lipid peroxide to form malondialdehyde (MDA) which can be detected in the myocardium. This study was to determine the level of exposure to toluene at low doses below the threshold that causes the increase in value of myocardial MDA and increase in the number of lipid vacuoles.

Methods: This study used a true experiment study. Thirty male Wistar rats aged 3 months weighing 150-200 g were randomly selected, divided equally per 1.6 ml of toluene exposure: 3.2 ml 6.4 ml; 12.8 ml and control. Administered by inhalation exposure to toluene spraying liquid into the tank, with the addition of doses per hour according to the calculation of the air flow and the volume of the aquarium for 4 hours per day until 4 consecutive days. In microscopic lipid vacuoles shifted more to the edge, counted in 10 visual field. Statistical analysis ANOVA and post hoc ANOVA on normally distributed data.

Results: The average value of MDA in the myocardium between exposure groups that look significantly different between exposure groups 12.8 ml with controls (p = 0.024), res. 12.8 ml with kel. Exposure 6.4 ml (p = 0.002) and res. 12.8 ml with kel. 3.2 ml (p = 0.002). While the average number of lipid vacuoles in the level of exposure no significant relationship (p = 0.248).

Conclusion: The difference between the mean level of exposure does not occur at exposures below the threshold value (50 ppm), there are visible differences in exposure to 12.8 ml (100 ppm) with other exposure. There was no increase in the number of lipid vacuoles in male Wistar rats.

Keywords: Toluene, Myocardium Malondialdehyde, Histopathology picture Myocardium, lipid vacuoles
INTRODUCTION

Toluene is an aromatic hydrocarbon with the formation of the chemical elements in which the hydrogen atoms of benzene is replaced by a methyl group (1). Toluene is a colorless liquid, clear, odorless at ambient temperatures such as benzene and a volatile liquid, flammable, and explosive. Toluene route of entry into the human body through the respiratory tract can, mouth, and skin. The main route of exposure is through inhalation of toluene, such as vapor in the ambient air, cigarette smoke, solvent abuse and household liquid materials. The main sources of toluene are released in the air is the combustion of fossil fuels [7].

Toluene is widely used both in industry and households. The use of toluene in industry is widely used as a solvent or as a base material, such as: paint solvents, thinners, inks, adhesives, pharmaceutical products, cosmetics, additives, pesticide industry, crude petroleum, industrial plastics, and synthetic fibers. While the use of toluene in their own households found in many disinfectants and glue [8].

Therefore, the use of toluene in the world is still very high, reaching 0.5 x 107 to 1 x 107 tonnes. In Europe needs the use of toluene in the industry as much as 2.38 million tons (2007), in North America needs as much as one million tons (2009), while in Asia needs toluene as many as 23 million tons (2006) [9]. Toluene production in 1994 in the USA is estimated at more than three million tons. While the usage data of toluene in the industry in Indonesia has yet to exist. According to the Agency for Toxic Substances and Disease Registry (ATSDR) 2011, workers exposed to toluene each year ranges from four to five million workers. Therefore, one of the world body made permissible exposure limits. American Conference Governmental Industrial Hygiene (ACGIH) has been set Threshold Limit Value (TLV) of 50 ppm in 2009. Indonesian government set a threshold limit value (TLV) is 50 parts toluene permillion (ppm) by the Indonesian National Standard (SNI) 19-0232 - 2005 [10].

Although widely used around the world, it is undeniable that toluene has a negative effect on health. Several studies have shown that toluene has a toxic effect on the broad human organ systems in the body, which include death and impaired systemic effect (respiratory organs, heart, eye, liver, kidney, musculoskeletal, hematologic-supernormal system, endocrine, skin, neurologic, reproduction, and weight loss). One of the vital organs that can be attacked by toluene is the human heart. In workers exposed to toluene, the organ can be impaired heart dysrhythmias, interstitial fibrosis and the formation of lipid vacuoles. This can cause a death to workers [6].

Reinhartd and his colleagues in 1973 showed that in several solvents including toluene, the myocardium is sensitive to adrenaline and become a significant factor against myocardial damage. Damage to the myocardium by Sikora and Gali (1967), can occur in severe poisoning toluene, whereas Tomaszewski (1978) showed junctional cardiac rhythm [11].

At the biomolecular level, which is lipophilic toluene can change the structure of cell membrane lipids and increase the value of lipid peroxidation. One marker of lipid peroxidation such an increase is the increase in the value of Malondialdehyde (MDA) myocardium that will be used in this study. Malondialdehyde (MDA) will form the Reactive Oxygen Species (ROS) resulting in oxidative stress in various tissues of the body, causing tissue damage, either reversible or irreversible. If exposure to toluene lasts longer, [8][9][10][11]. When toluene exposure lasts longer, then the cells of the heart (myocardium) may undergo necrosis and apoptosis processes that lead to cell death.

Recommendations NAB toluene in Indonesia is 50 ppm, but the determination is not based on existing research. The research looked at a picture histopathology lipid vacuoles, so it can not be done in humans (ethical considerations), then the experimental study conducted on male Wistar rats.

In the histopathological stage with HE staining under light microscope can be seen the early changes in the heart muscle. From the study of existing literature between toluene with myocardial cells that are only available subchronic exposure [8].

According Cosmopoint International Institute of Technology (CIIT) (1980) in mice exposed to 300 ppm of toluene for 24 months (6 hours / day) or rats and mice were given more exposure to 1200 ppm toluene for 24 months (6.5 hours / day) did not reveal any lesions on the heart picture. In pujanaan 2500 ppm toluene for 14-15 weeks (6.5 hours / day) there was a heavy increase in heart rat (National Toxic Program, 1990). [12] So the aim of this study to
see whether the early changes in the form of lipid vacuoles and whether the increase in value of myocardial MDA can be used as a marker of oxidative stress used lower exposure to toluene is 0 ppm, 12.5 ppm, 25 ppm, 50 ppm, 100 ppm with a shorter time is 14 days.

Test an increase in the value of MDA and early histopathological changes in the myocardium due to exposure to toluene will be performed in mice because mice have similarities with humans in the absorption, distribution, metabolism, and excretion of toluene.[19]

To detect early changes such as degeneration of lipids, in this study, investigators using light microscopy and hematoxylin eosin staining (HE). In mice, we have not found such effects in humans. Therefore, in this study, wanted to see the early histopathological changes in male Wistar rats.

As in the general toxicity studies, this study used Wistar rats to evaluate the cardiac toxicity of toluene. This study used a lower dose than the threshold value defined in humans at this time to see changes in the biomolecular level and histopathology. Thus, this study can contribute to tolerance toxicity data for the development of science and technology.

METHOD

The study design is a true experimental study. The selection of a simple random sample to consist of a control group and four groups of mice with different amount of exposure to 1.6 ml, 3.2 ml, 6.4 ml and 12.8 ml, respectively considered equivalent to 12.5 ppm, 25 ppm, 50 ppm, and 100 ppm. The samples were 20 male Wistar rats approximately 3 months old, weighing 200-250 grams each, there is no anatomical abnormalities, obtained from the Agency for Health Research and Development (Research and Development). Toluene is sprayed into the tank measuring 80 cm x 40 cm x 40 cm with a duration of 4 hours per day for 14 days.

Flowed into the aquarium bubbler air passing through every hour and added some liquid toluene so that the concentration remains constant. Environmental conditions in the aquarium is maintained at a temperature of 27-30.5 °C and 60-90% humidity with a fan in the middle giving the aquarium it is also to maintain the animal's physical condition and facilitate dispersion of toluene. Temperature and humidity gauges placed in the aquarium.

Quality assurance is done to avoid the bias that may arise from environmental factors, as well as errors in maintenance procedures, treatment, making preparations and reading the results. Collection data in two phases: pre-clinimatory to get the value as a reference standard in data collection and treatment phase. Examination of the value of malondialdehyde (MDA) myocardium using the thiobarbituric acid-reactive test substance (TBARS) method wills, carried out in the Laboratory of Biochemistry Faculty of Medicine calculated with units of mmol / mg. Histopathological examination of the myocardium is done by hematoxylin eosin staining (HE). Reading of the results is focused on all the cells of the myocardium with empty vacuoles which dominate the cell cytoplasm and nucleus moved to the peripheral cells.

Evaluation of the preparations done by 10 field of view with a magnification of 400x microscope, photographed with a light microscope equipped with a Nikon Eclipse E 600 photographic W. The results were analyzed or calculated with the help of software MBF Image J calculated that each cell has a fatty degeneration of the changes in myocardium.

This experimental study has passed the test of Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia (Faculty of Medicine) in October 2011.

Characteristics of the study sample can be seen with a descriptive analysis of the sample weight, the average mean temperature and average humidity environment. Statistical analysis to look at the value of myocardial MDA and lipid vacuoles number of each group begins with the data normality test, ANOVA test is used for normally distributed data and the Kruskal-Wallis test is used on data that were not normally distributed. Post hoc analysis was also performed to look at where the exposure group differences were found MDA value and number of lipid vacuoles.
RESULTS

Descriptive analysis of the characteristics of each male Wistar rats of weight, temperature and humidity in the aquarium shown in Table 1. Shows the mean differences between groups of mice body weight was not statistically significant (p = 0.281), by Kruskal-Wallis test, all sample have equal weight in each group. The difference between the average temperature in the aquarium of different groups was statistically significant (p < 0.001) and the mean differences between groups humidity in the aquarium statistically significantly different (p < 0.001).

Table 1: Characteristics of Animals Try Preview (Kruskal Wallis test)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat's Weight Loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>239.67</td>
<td>8.07</td>
<td>0.281</td>
</tr>
<tr>
<td>Exposure group 1.6 ml</td>
<td>5</td>
<td>237.8</td>
<td>6.35</td>
<td></td>
</tr>
<tr>
<td>Exposure group 3.2 ml</td>
<td>6</td>
<td>237.33</td>
<td>4.18</td>
<td></td>
</tr>
<tr>
<td>Exposure group 6.4 ml</td>
<td>6</td>
<td>239</td>
<td>5.62</td>
<td></td>
</tr>
<tr>
<td>Exposure group 12.8 ml</td>
<td>6</td>
<td>244</td>
<td>3.52</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temperature</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>30</td>
<td>29-31</td>
<td>0.000</td>
</tr>
<tr>
<td>Exposure group 1.6 ml</td>
<td>5</td>
<td>30</td>
<td>29-32</td>
<td></td>
</tr>
<tr>
<td>Exposure group 3.2 ml</td>
<td>6</td>
<td>30</td>
<td>29-32</td>
<td></td>
</tr>
<tr>
<td>Exposure group 6.4 ml</td>
<td>6</td>
<td>29</td>
<td>27-31</td>
<td></td>
</tr>
<tr>
<td>Exposure group 12.8 ml</td>
<td>6</td>
<td>29</td>
<td>27-31</td>
<td></td>
</tr>
</tbody>
</table>

The first picture is a picture of the control group myocardium, the image is not found increased lipid vacuoles. While in the second picture is a picture of the four groups myocardium (6.4 ml).

Table 2: Influence of the Level of Exposure to the Value of Myocardial MDA and Lipid Vacuoles in Each Group (One way ANOVA test)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Vacuoles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>0.779</td>
<td>0.116</td>
<td>0.248</td>
</tr>
<tr>
<td>Exposure group 1.6 ml</td>
<td>5</td>
<td>0.866</td>
<td>0.159</td>
<td></td>
</tr>
<tr>
<td>Exposure group 3.2 ml</td>
<td>6</td>
<td>1.011</td>
<td>0.232</td>
<td></td>
</tr>
<tr>
<td>Exposure group 6.4 ml</td>
<td>6</td>
<td>0.828</td>
<td>0.263</td>
<td></td>
</tr>
<tr>
<td>Exposure group 12.8 ml</td>
<td>6</td>
<td>0.763</td>
<td>0.173</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MDA Myocardium</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>0.112</td>
<td>0.055</td>
<td>0.029</td>
</tr>
<tr>
<td>Exposure group 1.6 ml</td>
<td>5</td>
<td>0.169</td>
<td>0.124</td>
<td></td>
</tr>
<tr>
<td>Exposure group 3.2 ml</td>
<td>6</td>
<td>0.175</td>
<td>0.072</td>
<td></td>
</tr>
<tr>
<td>Exposure group 6.4 ml</td>
<td>6</td>
<td>0.033</td>
<td>0.313</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Difference Value Change MDA Myocardium Significance between Groups (LSD Test)

<table>
<thead>
<tr>
<th></th>
<th>0 ml</th>
<th>1.6 ml</th>
<th>3.2 ml</th>
<th>6.4 ml</th>
<th>12.8 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ml</td>
<td>x</td>
<td>0.523</td>
<td>0.355</td>
<td>0.555</td>
<td>0.575</td>
</tr>
<tr>
<td>1.6 ml</td>
<td>0.523</td>
<td>x</td>
<td>0.255</td>
<td>0.197</td>
<td>0.113</td>
</tr>
<tr>
<td>3.2 ml</td>
<td>0.555</td>
<td>0.235</td>
<td>x</td>
<td>0.910</td>
<td>0.002</td>
</tr>
<tr>
<td>6.4 ml</td>
<td>0.484</td>
<td>0.197</td>
<td>0.910</td>
<td>x</td>
<td>0.002</td>
</tr>
<tr>
<td>12.8 ml</td>
<td>0.002</td>
<td>0.113</td>
<td>0.002</td>
<td>0.002</td>
<td>x</td>
</tr>
</tbody>
</table>

From Table 3 the Post Hoc ANOVA test, mean difference values obtained significant myocardial MDA (P < 0.05) between the control group and 12.8 ml exposure group (p = 0.024), between the exposure group and 12.8 ml 3.2 ml (p = 0.002) and group 6.4 ml with 12.8 ml (p = 0.002). It can be concluded that the changes in MDA myocardium especially in the exposure group 12.8 ml, where the difference between 12.8 ml with control, exposure group 3.2 ml, and exposure group 6.4 ml.

The mean number of lipid vacuoles, p value = 0.248 can be concluded that there is no significant difference between the groups.
Group IV (toluene exposure 6.4 ml)

Picture 1.
Histopathology Picture Myocardium

DISCUSSION
Temperature and humidity environment at the time of exposure is difficult to keep constant control so that there is some environmental conditions of each exposure group may not equal the influence at the time of the study, so that the efforts that have been made, among others, use a small fan, and temperature measuring instruments humidity in the aquarium, research conducted in the air-conditioned room with a temperature of 23 °C-25 °C, thus the effect of environmental heat stress can be controlled.

Malondialdehyde Myocardium
Myocardial MDA values *3* compared to control group may not equal the influence at the time of the study, so that the efforts that have been made, among others, use a small fan, and temperature measuring instruments humidity in the aquarium, research conducted in the air-conditioned room with a temperature of 23 °C-25 °C, thus the effect of environmental heat stress can be controlled.

Malondialdehyde Myocardium

Malondialdehyde (MDA) is one of the biological markers that can be detected in the blood and some tissues in the body are used to determine the increase in lipid peroxidation [51] with low exposure levels and in a short time is not an optimal effect on the value of MDA.

3. According Saturina and Edward (2004) exercise with high intensity and long duration shown to cause cell damage. Research conducted in 2008 Mashałach in rats given the workload of physical activity (swimming stress) with tail load 2% of the body weight of mice showed a significant increase in MDA values *3* compared to the control group. Research Misra et al in 2005 in mice that dianengan, with a time of 8 hours / day by swimming the length of 10 minutes followed by 30 minutes of rest during the 28 days of free radicals found in the treated group 235.27 mmol / mg tissue, whereas in the group without treatment 196.79 mmol / mg tissue. According Adiputra in 2008, start physical training physiological and biochemical responses are complex. Each movement begins with a rapid muscle anaerobic metabolism. Strength comes from the breakdown of ATP to ADP or AMP results and takes place in the mitochondria. The energy release is accompanied by the increased flow of electrons in a series of mitochondrial respiration resulting in the formation of reactive oxygen (O2-) and H2O2 and ATP formation efforts. Training tends to empty the ATP and ADP increase the amount which would stimulate the conversion of ADP catalysis and Xanthine Xanthine dehydrogenase into oxidase. Oxidase Xanthine dehydrogenase this will form free radicals (O2-). Formation of free radicals will cause an imbalance known as oxidative stress damage with the end result of free radicals proteins and DNA.

In this study, mice not given load, activity or physical training so that MDA in the myocardium has not been optimally formed.

Based on observations, the level of activity of Wistar rats showed differences in each group. In the group of 12.8 mL physical activity Wistar rats look more active than the other groups. This is one of the causes of
Differences in myocardial MDA results in the exposure group showed a 12.8 ml increase in the difference. In this study it was found that the exposure of 12.8 ml (100 ppm) toluene myocardium MDA reveal any differences with the control group, exposure to 3.2 ml and 6.4 ml. The exposure is exposure above the threshold value set in Indonesia by SNI 19-0232-2005 and the American Conference of Governmental Industrial Hygienists (ACGIH) 50 ppm (2009), while NAB Toluene 1000 ppm according to NIOSH, OSHA 200 ppm. Therefore, it is not found the lowest levels of toluene exposure below the threshold value which can affect the value of a male Wistar rat myocardium MDA.

Histopathology Picture Male Wistar Rats Myocardium

Bracken and Peterson in 1981, there were no histopathological abnormalities in mouse heart dipijan 4,000 ppm toluene for 3 hours / day in 8 weeks or in mice that dipijan 12,000 ppm for 70 minutes / day in 8 weeks. At the level of exposure lower in the longer time also did not reveal any changes in the histopathology abnormalities, such as the NTP study (1990), rats exposed to 1,200 ppm toluene for 24 months (6.5 hours / day) and also CITT (1980), existing results obtained showed no histopathological lesions in the rat heart associated with exposure to toluene of 300 ppm for 24 months (6 hours / day). According to the NTP (1990) in female rats exposed to 2,500 ppm of toluene for 14-15 weeks (6.5 hours / day) a change in the increase in heart weight.

In this study, the number of lipid vacuoles statistically in this study showed no significant difference in the mean. No changes in lipid vacuoles, probably caused by a number of relatively small exposure to toluene gave rise to the appearance of fatty or lipid vacuoles in the cells of the myocardium. Short exposure time (14 days with a time of 4 hours per day) may be a factor that causes the number of lipid vacuoles were not significantly different in the animal studies. In addition to the lack of activity can lead to the accumulation of fat tissue, it can cause the appearance of lipid vacuoles in myocardium. Changes in lipid vacuoles in Wistar rats are estimated to occur due to the formation of lipid vacuoles that are not optimal. Similarly, the composition of which has been controlled nutrition on food intake. So the results of this study, did not reveal any significant increase in lipid vacuoles due to exposure to toluene.

Limitations of this study is the absence of an appropriate tool for measuring the value of toluene in the aquarium during the exposure, so the value of toluene in the aquarium are measured into milliliters (ml). Calculation (conversion value) adjusted with toluene exposure aquarium volume and speed of air flow out so that a constant value for toluene exposure.

CONCLUSION

Toluene exposure led to the formation of Reactive Oxygen Species (ROS), thereby affecting the myocardium MDA values. The study groups, it can be used as markers of oxidative stress in myocardial damage. However, the mean difference between the level of exposure does not occur at exposure below the threshold value (50 ppm). Exposure levels above the threshold value (100 ppm) were observed mean difference exists at each level of exposure to the other.

Toluene exposure level of 12.5 ppm, 25 ppm, 50 ppm, 100 ppm and also given to male Wistar rats for 4 hours for 14 days has not been able to prove the absence of histopathological changes such as the increase in the number of lipid vacuoles in male Wistar rat myocardium.

Suggestion

1. To facilitate control of the value of toluene in the aquarium then it can use the autoregulatory circuit to automatically issue toluene parasite so that value can be maintained constant at the aquarium.
2. Further research is needed regarding the activity of test animals to be able to prove the value changes of the myocardium MDA and lipid vacuoles.
3. Need to check other biological markers to support this research by looking at an increase in lipid peroxidation against toluene, such as 4-HNE, 8-isoprostaglandin F2α, and TBARS.
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