Analyzis The Effect Of Antipsychotic Therapy On Levels Of Ast And Alt At Dr. Radjiman Widodiningrat Lawang Mental Hospital

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Abstract

Antipsychotics are a first-line therapy in schizophrenia that can improve the symptoms of psychosis. Long-term use of antipsychotics can cause liver damage or referred to as Drug Induced Liver Injury (DILI). The purpose of this study was to determine the relationship between the use of combination or single antipsychotics chlorpromazine compared to risperidone. The study design was carried out in a case-control manner with retrospective sampling from January to May 2023 at the Dr. Radjiman Wediodiningrat Lawang Mental Hospital. In this study, there were 56 medical records that met the inclusion criteria. The data were analyzed descriptively and analytically with the chi-square test. The descriptive picture of receiving single and combination chlorpromazine therapy had 22 respondents, while single and combination risperidone therapy had 34 respondents. The results were obtained that there was no effect of antipsychotic use on the incidence of DILI (p-value=0.752). Based on characteristic data, it is known that most patients fall into the normal category where the male sex is more dominant who experiences schizophrenia and the age distribution is approximately the same between 17 to 55 years.

Keywords: AST; ALT; antipsychotic; DILI

1. INTRODUCTION

Schizophrenia is a psychotic disorder that results in significant disability and has a profound impact on various aspects of social functioning, including family, education, and employment. It is estimated that 24 million people worldwide, or approximately 1 in 200 individuals, are affected by schizophrenia (World Health Association, 2022). According to the 2018 Basic Health Research data in Indonesia, approximately 7 out of 1000 households with members aged 15 and above have a family member with schizophrenia (Kemenkes RI, 2018). The management of schizophrenia patients is typically achieved through the administration of antipsychotic medications, which are designed to control symptoms, enhance the quality of daily life, and facilitate a good social life. (National Insitute of Mental Health, 2021)

Prior research has demonstrated that the use of haloperidol or chlorpromazine antipsychotics can lead to an elevation in aspartate aminotransferase (AST) and alkaline phosphatase (ALT) levels (Meiyanti et al., 2022). Similarly, other studies have shown that patients undergoing a combination therapy of risperidone and chlorpromazine exhibit an increase in AST and ALT levels (Ramdini, 2023). Similarly, other studies have yielded comparable results, indicating an elevation in AST and ALT levels in patients undergoing risperidone therapy. It is important to note that these patients exhibited abnormal liver

function prior to initiating risperidone treatment (López-torres dkk., 2014).

Drug-Induced Liver Injury (DILI) is defined as a hepatocellular injury caused by an adverse drug reaction. DILI manifests as an elevation in transaminase levels in the blood, which is identified during laboratory testing (Tandon et al., 2022). The objective of the liver is to serve as a biotransformation organ for xenobiotics, facilitating the conversion of metabolites into more polar compounds that can be more readily excreted (Andrade et al., 2019). Liver damage resulting from drug use can lead to increased reactivity of metabolites, which in turn can cause adverse effects (Tandon et al., 2022).

The objective of this study is to ascertain whether there is an influence of elevated AST and ALT levels in monotherapy or combination therapy with chlorpromazine compared to risperidone. Once the occurrence of increased AST and ALT levels is identified, healthcare professionals can evaluate the use of antipsychotic therapy in respondents with abnormal liver enzyme levels.

2. METHODS

Type and Research Design

The research design used was observational with a cross sectional study method. The data used is restrospective.

Research Design

The variables in this study include the independent variables, which are the use of single and combined chlorpromazine antipsychotics and single and combined risperidone. The dependent variable in this study is the increase in normal and abnormal AST and ALT levels with a value of >40 U/L. The characteristics of respondents in this study include age, gender, and other drugs besides antipsychotics used by patients.

Research Materials

The research material utilized in this study was derived from the medical records of patients at Dr. Radjiman Wediodiningrat Lawang Mental Hospital. The data employed for the period spanning January to May 2023 were obtained from the aforementioned medical records. Secondary data were procured from the medical records section through a brokerage agreement with a pharmaceutical installation, and were provided in the form of Excel documents.

Population dan Sample

The study population consisted of all patients diagnosed with schizophrenia at Dr. Radjiman Wediodiningrat Lawang Mental Hospital. The study population consisted of four distinct groups: (1) all patients who met the inclusion criteria, namely patients with a diagnosis of schizophrenia; (2) patients who received single or combined chlorpromazine therapy and single or combined risperidone therapy; (3) patients with an age range of 17-55 years; and (4) patients with AST and ALT lab results. This study has been granted ethical approval by the research hospital, with the approval number TK.02.04/D.XXXVII. 3.6/ 6522 /2023.

Data Analysis

The data analysis on the characteristics of the respondents and the incidence of increased AST and ALT levels were presented descriptively in the form of percentages. Furthermore, a statistical analysis was conducted to determine the relationship between single or combined chlorpromazine and single or combined

risperidone on the increase in AST and ALT levels using Chi-Square with SPSS 26 software.

3. RESULT AND DISCUSSION

A total of 56 samples met the inclusion criteria for this study. Of these, 22 respondents received single or combined chlorpromazine therapy, while 34 received single or combined risperidone therapy. In terms of antipsychotic use, 14 respondents exhibited elevated AST and ALT levels, while 42 demonstrated normal AST and ALT levels..

Table 1. The Utilization of antipsychotic medications in conjunction with levels of AST and/ALT.

Antipsychotic Medications		Levels of AST dan/ ALT (n=56)		Total
		Abnormal (n=14)	Normal (n=42)	
Klorpromazin	Single	0 (0%)	0 (0%)	22 (39,3%)
	Combination	5 (35,7%)	17 (40,5%)	
Risperidon	Single	0 (0%)	8 (19%)	34 (60,7%)
	Combination	9 (64,3%)	17 (40,5%)	

As evidenced by Table 1, combined risperidone therapy (64.3%) was associated with a higher incidence of AST and ALT elevations compared to single or combined risperidone therapy. These findings align with those of previous research studies, which have demonstrated that the combined use of risperidone is associated with an increased risk of AST and ALT elevation, potentially indicating a vulnerability factor for liver damage (Magfirah Harun et al., 2022).

The use of single or combined chlorpromazine therapy included 22 patients, of whom 5 (22.7%) exhibited abnormal AST and ALT levels, while 17 (77.3%) demonstrated normal AST and ALT levels. Risperidone therapy, administered either as a standalone treatment or in conjunction with other medications, was associated with abnormal AST and ALT levels in 9 (26.5%) respondents, while 25 (73.5%) respondents exhibited normal AST and ALT levels. As evidenced by the results presented in Table 3, the p-value of 0.752 indicates that the use of antipsychotics (either as a single agent or in combination) does not exert a statistically significant effect on the observed elevation in AST and ALT levels. This is due to the fact that the metabolic processes of chlorpromazine and risperidone result in the production of reactive metabolites. These reactive metabolites have the potential to bind covalently to cellular proteins, lipids, and nucleic acids, leading to disruption of cell structure and function. Protein binding to mitochondria can result in mitochondrial respiration impairment, which may contribute to superoxide radical anion leakage (Todorović Vukotić et al., 2021). The analysis findings suggest that typical and atypical antipsychotics may have a similar risk of elevating AST and ALT levels.

Table 2. The characteristics respondents with Levels of AST and ALT:

Characteristic of Respondents	Levels of AST dan/ ALT (n=56)	
Gender	Abnormal (%) (n=14)	Normal (%) (n=42)
Male	13 (92,9%)	28 (66,7%)
Female	1 (7,1%)	14 (33,3%)
Total	14 (100%)	42 (100%)
Age		
17-30 years	7 (50%)	11 (26,2%)
31-42 years	3 (21,4%)	18 (42,9%)
43-55 years	4 (28,6%)	13 (30,9%)
Total	14 (100%)	42 (100%)

Table 2 illustrates that males exhibited elevated AST and ALT levels, with an age range of 17-30 years (50%), as compared to the control group. The analysis of the relationship between increased AST and ALT levels with gender revealed no statistically significant correlation (p-value = 0.055). This may be attributed to the pairing of estrogen receptors, such as NR, ERA, and Erb, with membrane-bound G proteins (GPR30 or GPER), as well as membrane variations of ERA and Erb. These receptors are constitutively expressed in the liver at higher levels than in the reproductive organs. In hepatocytes, estrogen receptor alpha (ERα) plays a role in the process of lipogenesis. Three activated estrogens have been identified, namely E1 (estrogen), E2, and E3 (estriol). Dietary amino acids have been shown to activate hepatic estrogen receptors in a manner that is consistent with estrous cycle regulation. The differences in hepatic metabolism of dietary amino acids in females are related to hepatic receptors in the regulation of hepatic energy to support reproductive function. Estrogen receptor alpha (ERA) in the liver can sense fluctuations in circulating estrogen 2 (E2) levels, and the estrous cycle acts as a response to reproductive cues, thus modulating hepatic metabolism to adjust energy requirements. The isoform is responsible for the metabolic protective effects of estrogen against various liver injuries. The androgens, including testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenedione, androstenediol, and androsterone, play a significant role in the homeostatic orchestration of liver metabolism. Testosterone and DHT bind directly to their receptors, whereas the other four hormones act as pro-androgens, undergoing conversion to testosterone to utilize androgenic effects.

Androgens can bind directly to androgen receptors, thereby regulating the transcription of numerous genes and exerting non-genomic effects. These effects are mediated by the Mitogen-Activated Protein Kinase (MAPK) and Phosphatidylinositol-3-Kinase (PI3K/AKT) pathways, as well as by binding to membrane-associated androgen receptors or other membrane receptors, including the Epidermal Growth Factor Receptor (EGFR). In steatosis, androgens may reduce the risk of progression to non-alcoholic steatohepatitis (NASH) by downregulating pro-inflammatory cytokines. Conversely, in acute liver injury conditions, there is delayed resolution of necrosis damage and higher expression of

pro-inflammatory cytokines accompanied by slower inflammatory monocyte uptake, which is characterized by androgen receptor expression. Inflammatory monocyte uptake was modulated by the androgen receptor antagonist flutamide. (Sayaf et al., 2022).

Table 3. Analysis of the relationship between antipsychotic medications with levels of AST and/ALT.

Antipsychotic Medications	Levels of AST and/ALT (n=56)		Total	*p-value*	*Odd Ratio*
	Abnormal	Normal			
Chlorpromazine single and combination	5 (22,7%)	17 (77,3%)	22 (100%)	0,752	1,224
Risperidone single and combination	9 (26,5%)	25 (73,5%)	34 (100%)		
Total	14 (25%)	42 (75%)	56 (100%)		

In the age group 17-30 years, the increase in AST and ALT levels was observed to occur more frequently in the age range of 31-42 years (85.7%), followed by the age group 43-55 years (77.8%), and then the age group 17-30 years (58.8%). This can be attributed to an elevation in AST and ALT levels in adulthood, which may be attributed to lifestyle factors that can impact the liver, such as smoking and alcohol consumption. Additionally, genetic factors may also play a role. In contrast, in the elderly, liver damage can be influenced by a decline in the function of organs that are unable to perform optimally, potentially leading to complications in other organs (Sayaf et al., 2022).

In the analysis of the use of other drugs with increased AST and ALT levels, 14 respondents exhibited abnormal AST and ALT levels. Conversely, respondents who did not use other drugs did not demonstrate increased AST and ALT levels. In the analysis of the relationship between increased AST and ALT levels and the use of other drugs, no significant correlation was identified, with a p-value of 0.078. Some respondents reported using other drugs for the treatment or therapy of diseases other than the ones under study. A number of the other drugs used by respondents have the potential to cause an increase in AST and ALT levels. Benzodiazepine compounds, such as lorazepam and diazepam, have been demonstrated in the literature to exhibit solubility in fat and to undergo metabolic processes that can result in the increased reactivity of metabolites. The transformation of metabolites into reactive compounds can elevate the risk of developing cirrhosis due to an increase in the concentration of free metabolite compounds in the blood (Atrees & Rabie, 2021).

4. CONCLUSION

The findings of this study indicate that the administration of antipsychotics, either individually or in combination, to elevate AST and ALT levels carries an equivalent risk. The observed increase in AST and ALT levels was predominantly observed in subjects undergoing single or combined risperidone therapy.

It is important to note that this study has certain limitations. These include the exclusion of other potential risk factors that may contribute to liver damage, such as genetic predisposition, alcohol consumption, daily dose intake, comorbidities, and immunological factors.

5. ACKNOWLEDGEMENTS

The research team would like to express its gratitude to Dr. Radjiman Wediodiningrat of Lawang Mental Hospital for granting permission to conduct the study.

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