OPEN ACCESS Pharmacologia

ISSN 2044-4648
DOI: 10.5567/pharmacologia.2018.169.173

Research Article
Effect of Zidolam (Zidovudine and Lamivudine) on Liver Enzymes and Blood Glucose in Adult Wistar Rats of Both Sexes

[1]Osonuga Ifabunmi Oduyemi and [2]Adenowo Thomas Kehinde

[1]Department of Physiology, Olabisi Onabanjo University, Sagamu Campus, Sagamu, Nigeria
[2]Department of Anatomy, Olabisi Onabanjo University, Sagamu Campus, Sagamu, Nigeria

Abstract

Background and Objective: Zidolam is an antiretroviral combination therapy for the treatment of HIV infection. This study investigated the impact of highly active anti-retroviral (HAART) on the liver enzymes and blood glucose of adult Wistar rats of both sexes. **Materials and Methods:** Thirty Wistar rats with body weight (b.wt.,) of 150-230 g were used for the 2-phase study. Solution of the drug in sterile water was administered via oral cannula to the 2 groups of 10 rats (5 males and 5 females) each at daily dose of 1.29 mg/100 g b.wt., respectively for 21 days during phase I. Phase II was a recovery study involving 10 rats (5 males and 5 females) exposed to dose regimen as in phase I and sacrificed after 21-day withdrawal of treatment. The control group of 10 animals (5 males and 5 females) was given sterile water ad-libitum. Serum liver enzymes were determined using kits obtained from Randox Laboratories Ltd, UK. Blood from the cut-tips of the tails of the animals were obtained and glucose values were determined using glucometer. **Results:** Zidolam caused significant increase ($p<0.05$) in the liver enzymes: serum pyruvate aminotransferase, serum alkaline phosphatase and serum alanine aminotransferase as well as in blood glucose of the animals. Discontinuation of the drug use however caused gradual recovery of the values of the liver enzymes but the reverse was the case in blood glucose level where there was an increase in the values obtained. **Conclusion:** The results suggested that Zidolam could induce hepatotoxicity and diabetics in the treated animals and by extension man.

Key words: Zidolam, liver enzymes, blood glucose, wistar rats, anti-retroviral therapy, hepatotoxicity

Citation: Osonuga Ifabunmi Oduyemi and Adenowo Thomas Kehinde, 2018. Effect of zidolam (zidovudine and lamivudine) on liver enzymes and blood glucose in adult wistar rats of both sexes. Pharmacologia, 9: 169-173.

Corresponding Author: Osonuga Ifabunmi Oduyemi, Department of Physiology, Olabisi Onabanjo University, Sagamu Campus, Sagamu, Nigeria
Tel: +2348034840747

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Human Immunodeficiency Virus is an RNA retrovirus, infectious agent that causes acquired immunodeficiency syndrome (AIDS), a disease that leaves a person vulnerable to life-threatening infections. Human Immunodeficiency virus and Acquired Immunodeficiency Syndrome remains a significant problem that affects all sectors of the population[1]. HIV/AIDS remains the greatest public health crises in the world today and is the 4th leading cause of mortality in the world[2]. Scientists have identified two types of this virus. HIV-1 is the primary cause of AIDS worldwide. HIV-2 is found mostly in West Africa[3]. In 2004, the World Health Organization estimated that almost 40 million people were living with AIDS and that women and children constituted approximately half that total number[3]. Already, 18.8 million people around the world have died of AIDS, 3.8 million of them children. Nearly twice that many-34.3 million are now living with HIV, the virus[3]. Since the early 1990s, it has been clear that HIV would help undermine development in countries badly affected by the virus[3]. These effects are becoming increasingly visible in the hardest-hit region of all, sub-Saharan Africa, where HIV is now deadlier than war itself: in 1998, 200,000 Africans died in war but more than 2 million died of AIDS. AIDS has become a full-blown development crisis[3].

HIV/AIDS is chronic lifelong disease with no known cure and therefore, people living with HIV (PLHIV) have to be followed medically for the rest of their lives[4,5]. The core component of treatment and care of PLHIV is provision of anti-retroviral treatment (ART). Anti-retroviral therapy refers to the use of pharmacologic agents that have specific inhibitory effects on HIV replication. Optimal ART increases the length and quality of life of HIV-infected patients and reduces the onward transmission of the virus. Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV. When several such drugs, typically three or four, are taken in combination, the approach is known as highly active antiretroviral therapy, or HAART[6,7] and the use of HAART has resulted in a marked improvement in prognosis of HIV disease[8].

In 1984, it became clear that HIV was the known cause of acquired immunodeficiency syndrome (AIDS). Not quite long after this knowledge, drugs that could devastate the virus were placed on clinical trials[9].

There are currently more ARV drugs and their clinical effectiveness has improved remarkably. Fischl *et al.*[10] explained that drug development for anti-HIV therapies rests on our knowledge of replication cycle of the virus. Thus, some sustained inhibition of viral replication might lead to partial reconstruction of the immune system and a substantial reduction in the risk of clinical disease progression. Most importantly, blocking the initial phases of viral replication prevents infection of new cells. Two groups of antiretroviral compounds that interfere with HIV reproduction are reverse transcriptase inhibitors and protease inhibitors.

Recent advances in the treatment of HIV-1 infection involving co-administration of reverse transcriptase and protease inhibitors to achieve near-complete suppression of HIV-RNA concentrations have led to considerable improvements in life expectancy of infected individuals[11,12]. Highly active antiretroviral therapy (HAART), i.e., the use of aggressive combination antiretroviral regimens consisting of reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) has become the standard of care[13,14].

Zidolam is an antiretroviral drug belonging to the antiretroviral group called nucleoside analogue reverse transcriptase inhibitors (NRTIs). It is used in antiretroviral combination therapy for the treatment of HIV infection. It reduces the amount of HIV in the body and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cells that plays an important role in maintaining a healthy immune system to help fight infection.

Not much work has been done on effects of antiretroviral therapy on blood glucose but in 2004, Figuerio-Filho *et al.*[15] conducted a test to experimentally evaluate the diabetogenic effects of anti retroviral drugs on pregnant wistar rats and perinatal effects on the offspring. Using zidovudine (ZDV), lamivudine (3TC) and nelfinavir (NFV), they concluded that the anti retroviral drugs interfered in carbohydrate metabolism of pregnant rats and reduced the number of fetuses. 3TC caused less maternal body weight gain, decreased fetus weight and lactate and insulin levels and increased serum glucagon. Hence, the need of this research to further investigate the relationship between anti retroviral therapy and blood glucose level as well as liver enzymes in adult albino rats of both sexes. The aim of this study was to determine the effects of Zidolam on liver enzymes and blood glucose in adult Wistar rats of both sexes.

MATERIALS AND METHOD

Animals: Thirty adult Wistar strain rats of both sexes (15 females and 15 males) weighing between 180 and 220 g were obtained from author's own departmental animal house and were housed five animals per cage at room temperature where they were acclimatized for a period of 7 days. The study was approved by departmental animal ethical

committee. The animals were fed with standard rat pellets (Ladokun Feeds Nig. Ltd.) and water ad libitum.

Animal ethics: All procedures involving animals in this study confirmed to the guiding principles for research involving animals as recommended by the Declaration of Helsinki and the Guiding Principles in the Use of Animals[16].

Experimental procedure: The study was divided into two phases involving the use of drug and sampling in the first phase, as well as drug administration, recovery period followed by sample collection in the second phase. Zidolam was obtained from General Hospital, Ijebu Igbo, Nigeria. The drug was administered orally at therapeutic (human dose was calculated down to rats weights) (T) dose of 1.29 mg per 100 g b.wt., respectively to the rats daily for 21 days.

Phase 1 entails the use of 10 rats (5 males and 5 females). Each rat in the group was treated with 1.29 mg/100 g b.wt., of zidolam daily for 21 days.

Phase 2 was a recovery study involving ten rats (5 males and 5 females).The animals were given 1.29 mg/100 g b.wt. of zidolam each for 21 days and allowed to recover from the treatment for another 21 days.

There was a group of 10 rats (5 males and 5 females) given sterile water throughout the study and these serve as the control (C) in both phases.

Analytical procedure: The rats were weighed prior to treatment and at the end of each phase to obtain differential weight gains (if any).

Serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and serum alkaline phosphatase (SALP) were determined using kits (from Randox Laboratories, Ltd., UK) according to manufacturer's instructions.

Blood from the cut-tips of the tails of 15 males and 15 females' rats were obtained and blood glucose values were determined using glucometer.

Statistical analysis: All calculations were done using the SPSS-V15 statistical software package[17] for analysis of the data. The data were presented as Means±Standard deviation (SD) and statistical analysis carried out using the Student's t-test and One-Way ANOVA. Differences were considered to be of statistical significance at an error probability of less than 0.05 ($p<0.05$).

Table 1: Effect of Zidolam on liver enzymes

Groups	SALP (U L^{-1})	SGPT (U L^{-1})	SGOT (U L^{-1})
Control group male	0.04±0.02	0.06±0.01	0.04±0.02
Control group female	0.02±0.01	0.09±0.02	0.03±0.02
Test group male	0.07±0.01*	0.11±0.02*	0.09±0.03*
Test group female	0.05±0.02*	0.13±0.03*	0.09±0.04*
Recovery group male	0.04±0.01*	0.08±0.02*	0.06±0.04*
Recovery group female	0.05±0.02*	0.09±0.02*	0.05±0.01*

*p<0.05

Table 2: Effect of Zidolam on blood glucose

Groups	Blood glucose
Control group male	91.61±21.7
Control group female	101.00±14.32
Test group male	125.60±10.88*
Test group female	148.80±8.17*
Recovery group male	148.40±46.55*
Recovery group female	157.40±26.32*

*p<0.05 (p is significant at p<0.05)

RESULTS

Effect of Zidolam on liver enzymes: The results were shown in Table 1.

Administration of Zidolam at 1.29 mg/100 g of b.wt./day for 21 days significantly ($p<0.05$) increased the values of SGOT, SGPT and SALP in both male and female rats and these values gradually return to normal values after allowing the rats to recover from effects of the drug.

Effect of zidolam on blood glucose: The results were shown in Table 2.

Administration of zidolam at 1.29mg/100 g of b.wt./day for 21 days significantly increased ($p<0.05$) the values of blood glucose in both male and female rats.

The values of the recovery groups increased significantly ($p<0.05$) when compared to the control groups.

From Table 2, the values of the recovery groups failed to reduce but continue to increase even after zidolam had been withdrawn for 21 days.

DISCUSSION

This investigation demonstrated that administration of Zidolam to rats significantly ($p<0.05$) increased the liver enzymes of the animals (Table 1).

Increase in liver enzymes such as serum glutamate pyruvate transaminase (SGPT) and serum glutamate oxaloacetate transaminase (SGOT) are common findings in liver toxicity[18]. Elevated liver enzymes are signs of liver inflammation and may be a warning of progressive liver disease. Liver disease is a major cause of morbidity and mortality in HIV infected persons[19]. Abnormalities in liver

function are common and may be caused by HIV itself. Co-infection with hepatitis viruses increases the risk of liver toxicity while taking antiretroviral therapy. Hepatotoxicity is a serious complication in patients taking HAART [20]. The present study has shown that there was a significant increase in all the measured liver enzymes indicating some degree of damage to the tissues in the liver. The study also demonstrated that the noticeable effect is reversible as observed in the recovery group and this is important to patients taking the drug as they could readily recover from adverse effects on liver. This reversal is time dependent and this may not be unconnected with plasma clearance of the drug leading to secretion. Elevated liver enzymes may be due to HAART or to other risk factors such as hepatitis co-infection[18-20]. The different components of HAART are each associated with different risks of liver toxicity. Most drugs are metabolized by cytochrome P450 enzymes in the liver and this may be affected by liver disease[21]. The mechanisms for drug-induced liver injury include dose-dependent toxicity, hypersensitivity reactions, idiosyncratic reactions, mitochondrial toxicity and immune reconstitution. The present study has shown that there was a significant increase in all measured liver enzymes indicating some degree of damage to the tissues in the liver.

This investigation also demonstrated that administration of Zidolam to rats significantly ($p<0.05$) increased the blood glucose of the animals. The increased in blood glucose failed to decline even after the animals were allowed to recover from drug effects and this might further complicate the health hazards being faced by the patients .

Before the onset of the use of highly active anti-retroviral drugs, HIV infection was thought to be protective against development of diabetes mellitus[22].

But with the advent of highly active antiretroviral therapy, a new dysmetabolic syndrome emerged [23] and it has variable expressions and includes insulin resistance, visceral adiposity, peripheral lipodystrophy and glucose intolerance.

Several studies have shown an increased risk of diabetes among HIV infected individual on highly active antiretroviral therapy (HAART)[24, 25].

The mechanism by which antiretroviral therapy (ART) drugs induced diabetic is not clear, it has been shown that indinavir dramatically inhibits glucose uptake in a dose dependent manner in adipocytes by selectively inhibiting the glut 4 transporter functions[26].

Also it has been found by Caron *et al.*[27] that indinavir down regulates peroxisome proliferators activated receptor gamma receptor in adipocytes.

In 2004, Figuerio-Filho *et al.*[15] conducted a test to experimentally evaluate the diabetogenic effects of anti retroviral drugs on pregnant Wistar rats and perinatal effects on the offspring. Using zidovudine (ZDV), lamivudine (3TC) and nelfinavir (NFV), they concluded that the anti retroviral drugs interfered in carbohydrate metabolism of pregnant rats and reduced the number of fetuses. 3TC caused less maternal body weight gain, decreased fetus weight and lactate and insulin levels and increased serum glucagon.

CONCLUSION

The study demonstrated that Zidolam is injurious to the liver and it is also diabetogenic hence it should be used with caution and under supervision of a qualify health practitioner.

The study was able to prove that there is need to monitor the blood glucose and liver enzymes of patients undergoing treatment using Zidolam by experienced medical practitioner. The monitoring should continue even after the treatment has stopped in order to control any unwanted side effects of the drug.

SIGNIFICANCE STATEMENT

The present study revealed that the high level of blood glucose observed during treatment stage failed to reduce even during period of recovery. Diabetes is a chronic disorder characterized by high levels of glucose in the blood and is a common disorder affecting individuals of all ages. Since the drug is diabetogenic without the presence of human immunodeficiency virus in Wistar rats used for the experiment, it means zidolam can induce diabetics in human beings hence patients on ART should be treated for increased in blood glucose level in order to combat this unwanted side effects of the drug.

REFERENCES

1. Nsimba, S.E.D., H. Irunde and C. Comoro, 2010. Barriers to ARV Adherence among HIV/AIDS positive persons taking anti-retroviral therapy in two Tanzanian regions 8-12 months after program initiation. J. AIDS Clin. Res., Vol. 1. 10.4172/2155-6113.1000111
2. Guha, P. and P. Sardar, 2011. Prevalence of paediatric HIV infection in Eastern India-first report. J. AIDS Clin. Res., Vol. 2. 10.4172/2155-6113.1000127
3. UNAIDS., 2000. Report on the Global HIV/AIDS Epidemic. Joint United Nations Programme on HIV/AIDS.
4. Palella, Jr. F.J., K.M. Delaney, A.C. Moorman, M.O. Loveless and J. Fuhrer *et al.*, 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N. Engl. J. Med., 338: 853-860.

5. Sterne, J.A., M.A. Hernan, B. Ledergerber, K. Tilling and R. Weber *et al*., 2005. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: A prospective cohort study. Lancet, 366: 378-384.
6. Dybul, M., A.S. Fauci, J.G. Bartlett, J.E. Kaplan and A.K. Pau, 2002. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents: The panel on clinical practices for treatment of HIV. Ann. Internal Med., 137: 381-433.
7. Miguez, M.J., R. Rosenberg, X. Burbano and R. Malow, 2011. Cholesterol as a mediator of alcohol-induced risks for respiratory disease hospitalizations among people living with HIV. J. AIDS Clin. Res., Vol. S1. 10.4172/2155-6113.S1-001
8. Pinola, M., A. Lazzarin, A. Antinori, G. Carosi, G. Di Perri and M. Moroni, 2010. Lopinavir/ritonavir + tenofovir dual therapy versus lopinavir/ritonavir-based triple therapy in HIV-infected antiretroviral naive subjects: The Kalead study. J. Antivir. Antiretrovir., 2: 056-062.
9. Cohen, J., 1993. How can HIV replication be controlled? Science, 260: 1257-1257.
10. Fischl, M.A., C.B. Parker, C. Pettinelli, M. Wulfsohn and M.S. Hirsch *et al*., 1990. A randomised controlled trial of reduced daily dose of Zidovudine in patients with AIDS. N. Eng. J. Med., 323: 1009-1014.
11. Temesgen, Z. and A.J. Wright, 1997. Recent advances in the management of human immunodeficiency virus infection. Mayo Clin. Proc., 72: 854-859.
12. Pande, P.P., 2009. Computational approach towards designing potential HIV inhibitors. J. Antivir. Antiretrovir., 1: 082-085.
13. Stanley, S.K., J.E. Kaplan, A. Fauci, J. Bartlett and E. Goosby *et al*., 1998. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. MMWR Recomm. Rep., 47: 42-82.
14. St. Clair, M.H., K.N. Pennington, J. Rooney and D.W. Barry, 1995. *In vitro* comparison of selected triple-drug combinations for suppression of HIV-1 replication: The Inter-Company Collaboration Protocol. J. Acquir. Immune Defic. Syndr. Hum. Retrovirol., 2: S83-S91.
15. Figueiro-Filho, E.A., G. Duarte, P. El Beitune, S.M. Quintana and A.C. Marcolin, 2004. Diabetogenic effect of antiretroviral drugs on pregnant wistar rats. Rev. Bras. Ginecol. Obstet., 26: 31-36.
16. APS., 2002. Guiding principles for research involving animals and human beings. Am. J. Physiol.-Regul. Integr. Comp. Physiol., R283: R281-R283.
17. Norusis, M.J., 1998. SPSS/PC+ for Windows, Base and Advanced Statistics User's Guide. Version 11.0. Statistical Packages for Social Sciences, Chicago, IL.
18. Pugh, A.J., A.J. Barve, K. Falkner, M. Patel and C.J. McClain, 2009. Drug-induced hepatotoxicity or drug-induced liver injury. Clin. Liver Dis., 13: 277-294.
19. Kontorinis, N. and D. Dieterich, 2003. Hepatotoxicity of antiretroviral therapy. AIDS Rev., 5: 36-43.
20. Abrescia, N., M. D'Abbraccio, M. Figoni, A. Busto, A. Maddaloni and M. de Marco, 2005. Hepatotoxicity of antiretroviral drugs. Curr. Pharm. Des., 11: 3697-3710.
21. Bonacini, M. and I. Inductivo-Yu, 2008. Highly active antiretroviral therapy-induced liver injury. Curr. Drug Saf., 3: 4-13.
22. Salehian, B., J. Bilas, M. Bazargan and M. Abbasian, 2005. Prevalence and incidence of diabetes in HIV-infected minority patients on protease inhibitors. J. Natl. Med. Assoc., 97: 1088-1092.
23. Carr, A., K. Samaras, S. Burton, M. Law, J. Freund, D.J. Chisholm and D.A. Cooper, 1998. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS, 12: F51-F58.
24. Kino, T., M. Mirani, S. Alesci and G.P. Chrousos, 2003. AIDS-related lipodystrophy/insulin resistance syndrome. Horm. Metab. Res., 35: 129-136.
25. Bakari, A.G., F. Sani-Bello, M.S. Shehu, A. Mai, I.S. Aliyu and I.I. Lawal, 2007. Anti-retroviral therapy induced diabetes in a Nigerian. Afr. Health Sci., 7: 133-135.
26. Murata, H., P.W. Hruz and M. Mueckler, 2000. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. J. Biol. Chem., 275: 20251-20254.
27. Caron, M., M. Auclair, C. Vigouroux, M. Glorian, C. Forest and J. Capeau, 2001. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation and induces insulin resistance. Diabetes, 50: 1378-1388.