Valley International Journals
Open Access Journal

INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND CLINICAL INVENTIONS
Volume 2 issue 01 2015 page no. 656-661 ISSN: 2348-991X
Available Online At: http://valleyinternational.net/index.php/our-jou/ijmsci

Effects Of Co – Administration Of Caffeinated Paracetamol And Artesunate On The Liver Enzymes Of Guinea Pigs.

C.O.Agbapajulu[1] MB,BS, Msc , E. Okonkwo[2] MLS

[1] Ozioma Hospital and Maternity,Box 343, Ihiala, Anambra State, Nigeria.
08034235382 Email:chibuzooliver@gmail.com
&
[2] Heartland Diagnotics Center, Okporo Rd, Amaifeke, Orlu, Imo state, Nigeria.
08032963277 Echerem4luv@gmail.com

Abstract: ***The effects of co-administration of caffeinated paracetamol and artesunate on the liver enzymes Alanine aminotransferase, (ALT), Aspartate aminotransferase (AST) and Alkaline phosphatase (ALP), of guinea pigs were studied. The study is aimed at investigating the possible toxic potentials of Caffeinated paracetamol and artesunate on the liver enzymes of guinea pigs. 24 guinea pigs were used and divided into 4 groups with 6 guinea pigs in each group. Group 1 served as the control, group 2 was given caffeinated paracetamol and group 3 was given artesunate. While group 4 was given co-administration of caffeinated paracetamol and artesunate according to their respective body weight. The Liver enzymes of ALP, ALT and AST were estimated using TECO DIAGNOSTIC KIT. The results obtained were statistically analyzed using students T- Test distribution. When the ALT, AST and ALP levels (30.94±13.26)u/l, (19.15±9.43)u/l, and (37.50±6.92)u/l of the group 2 were compared with the ALT, AST and ALP levels (26.52±5.10)u/l, (29.46±19.54)u/l, and (35.42±6.98)u/l of the control group, there was no significant difference (P>0.05). When the ALT, AST and ALP (23.57±8.33)u/l, (25.05±14.81)u/l and (35.42±3.36)u/l of the groups was compared with the ALT, AST and ALP (26.52±5.10)u/l, (29.46±19.54)u/l and (35.42±6.98)u/l of the control group there was no significant difference (P>0.05). Finally when the ALT, AST and ALP (29.46±12.15)u/l, (20.63±8.33)u/l and (29.17±2.76)u/l, of the group 4 was compared with the ALT, AST and ALP (26.52±5.10)u/l, (29.46±19.54)u/l and (35.42±6.98)u/l of the control group of the guinea pigs, there was no significant difference (P>0.05). Study suggests there were no hepatotoxicity /or hepatocellular damage on the liver guinea pigs.***

Keywords: Caffeinated Paracetamol, Artesunate, Guinea Pig, Liver Enzymes

I. INTRODUCTION

Caffeinated paracetamol is the product of the active ingredients of paracetamol and caffeine. The active ingredients exert their effect by unrelated pharmacological mechanisms. Paracetamol which is also called acetaminophen is used as an over the counter analgesic and mainly for the relief of pains, headache, and other minor pains. It is referred to as an analgesic (pain reliever) and antipyretic (fever reducer) (*Aronoff et al.,* 2006). Paracetamol is considered safe for

human consumption but at recommended dosage to avoid toxicity. However, acute overdose can cause potentially liver damage.. Oral administration of paracetamol is rapidly adsorbed from the gastro-intestinal tract, but when taken in excess can be fatal and leads to toxicity; it can result in liver necrosis. The use of sulfhydyl drugs can help reverse these effects *(Allen,* 2005). Paracetamol toxicity is the foremost cause of acute liver failure in the western world.

Caffeine which was discovered in the eighteenth century by some scientists is the major constituent of a general and widely consumed beverage called coffee. It is a mild stimulant. It is highly popular worldwide especially in German where the name Kaffee was named by a German scientist (*Baumann,* 1997).

Cirrhosis is a major correlate of hepatocellular carcinoma and the relation between coffee drinking and the risk of primary liver cancer has been examined in at least two studies (*Kummer,* 2003).

Coffee oil raises serum levels of the liver enzyme alanine aminotransferase (ALT) and to lesser extent, aspartate aminotransferase (AST). Elevation of these liver enzymes may indicate injury of hepatocytes (*Shermann,* 1999). ALT is predominantly present in the cytosol of hepatocytes and AST is predominantly present in the mitochondria. When hepatocytes sustain damage to their membrane, ALT is released from the cytosol, whereas when hepatocytes sustain more severe damage, AST is released from the mitochondria. When AST levels are more increased than ALT levels this could indicate obstruction of the bile duct or alcohol abuse *(Sherman,* 1999).

However, co-administration of paracetamol using fixed ratio drug is increasingly gaining popularity. Caffeine acts as an analgesic adjuvant which enhances efficacy of paracetamol.
Despite the benefit of rapid analgesic effect and the probable decrease in toxicity, co-administration with these agents is still a cause of concern *(Lawrence et al.,* 2009).

Artesunate (ART), a dihydroartemisinin-10-α hemisuccinate is a water soluble semi-synthetic derivative of artemisinin with a molecular weight of 384.4 *(Abdin et al., 2003; Efferth et al.,* 2007). Artesunate and artemisinin derivatives have been reported to be effective against both drug-resistant and cerebral malaria-causing strains of Plasmodium falciparum *(Abdin et al.,* 2003).

This study is aimed at investigating the possible toxic potentials of Caffeinated paracetamol and artesunate on the liver enzymes of guinea pigs.

II. MATERIALS AND METHODS

A. Drugs

i. Caffeinated Paracetamol (panadol extra tablet) used for the study was manufactured by Emzor pharmaceutical industries limited Lagos, Nigeria**.**

ii. Artesunate Tablet: was manufactured by CIPLA limited, MIDC patalganga M.S 410220 INDIA. Both drugs were bought from Ucheson pharmaceutical Ltd, Ihiala, Anambra State. The combination for the administration to the guinea pigs was obtained on the basis of their body weights.

B. Animals

The guinea pigs weighing 170-200g were all purchased from Egbe ventures, Ubaheze Awo-idemili, Imo State, and were transported in a ventilated carton to a Standard (private) animal house. They were kept under Standard Laboratory Conditions, were fed with standard feed from top

feeds limited, Sapele, Nigeria. They were also given water in a plastic bottle for two weeks to attain a very good body weight once in every 24hours and also to get acclimatized with the environment. They were divided into 4 groups for experimentation.

C. Experimental design

The 24 guinea pigs were divided into four experimental groups of 6 in each group which were all fed with normal diet and water for 17 days.

Group 1: received the normal diet and water only for 17 days

Group 2: received normal diet, water and 7.70mg/1.5ml of panadol extra (caffeinated paracetamol) for 3 days

Group 3 Received normal diet, water and 0.5mg/1 ml of Artesunate for 3 days.

Group 4 received normal diet, water, 7.70mg/1.5ml of panadol extra (caffeinated paracetamol) and 0.5mg/1ml of Artesunate co-administered for 3 days.

D. Route of drug Administration

The route of drug administration was oral and this was done by using a syringe.

E. Blood Collection

24 hours after the last dose were administered; the animals were anasthesized with chloroform vapour, quickly brought out of the jar and sacrificed. Whole blood was collected by cardiac puncture from each animal into clean dry test tubes. The blood was allowed to stand for about 15 minutes to clot and further spun in a centrifuge at 4000 rpm for 10 minutes. Serum was separated from the clot with Pasteur pipette into sterile sample tubes for the measurements of liver enzymes (Alanine aminotransferases, Aspartate aminotransferases and Alkaline phosphatases).

F. Laboratory procedures

All reagents were commercially purchased and manufacturer's standard operating procedures (SOPs) were strictly adhered to. Commercially prepared kits for the liver enzyes (ALT, AST and ALP) were purchased from Teco Diagnostic Ltd.

III. STATISTICAL ANALYSIS

All values were expressed as mean ± standard deviation. The statistical analysis was carried out using the students't-test distribution to detect differences between the experimental groups of full variables. Tests with probability values <0.05 being considered statistically significant while tests with probability value >0.05 were considered statistically not significant.

IV. RESULTS AND ANALYSIS

TABLE I: COMPARISON OF THE MEAN CHANGES IN BODY WEIGHT BEFORE AND AFTER ADMINISTRATION OF THE DRUGS.

All values were recorded in mean ± standard deviation

Groups	Initial weight	Final weight	P-value
Control	182.50±7.50	189.17±6.07	P>0.05
Caffeinated Paracetamol (panadol extra)	196.67±4.71	187.50±5.59	P<0.05
Artesunate	195.83±4.49	186.67±5.53	P<0.05
Caffeinated Paracetamol And Artesunate	189.17±8.37	177.50±8.04	P<0.05

In table I above, statistical analysis shows no significant differences (P>0.05) in the final weights of the guinea pigs (control group 1) when compared with the initial weight of the same control group of the guinea pigs. There was a significant decrease (P<0.05) in the final weight

of the group 2, group 3 and group 4 when compared with their respective initial weights.

TABLE II: COMPARISON OF THE MEAN SERUM VALUES OF ALT, AST AND ALP OF THE CONTROL GROUP AND GROUP 2 OF THE GUINEA PIGS.

All values were recorded in mean ± standard deviation

Parameters	Control	Group 2	P-value
ALT (u/l)	26.52±5.10	21.94±13.26	P>0.05
AST (u/l)	29.46±19.54	25.15±9.43	P>0.05
ALP (u/l)	35.42±6.98	27.50±6.92	P>0.05

Table II above shows a decrease between the control group values of ALT, AST and ALP when compared with group 2 (caffeinated paracetamol) of the guinea pigs) but there was no significant differences (P>0.05).

TABLE III: COMPARISON OF THE MEAN SERUM VALUES OF ALT, AST AND ALP OF THE CONTROL GROUP AND GROUP 3 OF THE GUINEA PIGS

All values were recorded in mean ± standard deviation

Parameters	Controls	Group 3	P-value
ALT (u/l)	26.52±5.10	23.57±8.33	P>0.05
AST (u/l)	29.46±19.54	25.05±14.81	P>0.05
ALP (u/l)	35.42±6.98	35.42±3.36	P>0.05

Table III above, statistically shows no significant differences, (P>0.05) between the control group values of ALT, AST and ALP when compared with the group 3 of the guinea pigs.

TABLE IV: COMPARISON OF THE MEAN SERUM VALUES OF ALT, AST AND ALP IN CONTROL GROUP AND GROUP 4 OF THE GUINEA PIGS.

All values were recorded in mean ± standard deviation

Parameters	Control	group 4	P-value
ALT (u/l)	26.52±5.10	29.46±12.15	P>0.05
AST (u/l)	29.46±19.54	20.63±8.33	P>0.05
ALP (u/l)	35.42±6.98	29.17±2.76	P>0.05

Table IV above, statistically shows no significant differences (P>0.05) between the control group values of ALT, AST and ALP when compared with the group 4 of the guinea pigs.

V. DISCUSSION

The study revealed a decrease in the levels of ALT, AST and ALP (group 2) when compared with the control group, although there was no significant differences (p>0.05). This is in agreement with the work of *(Aronoff et al.,* 2006),

where serum enzyme activities decreases following administration of caffeinated paracetamol in normal dosage.

In response to group 3 (guinea pigs which was given normal diet, water and 0.5mg/1ml of artesunate), there was no significant differences (P>0.05) in the levels of ALT, AST and ALP when compared with the control group. This is similar to the study of (*Taylor, and White (2004), in* which artesunate does not cause any damage to the liver when administered in a normal dosage. This insignificant difference suggests that there were no hepatotoxicity or hepatocellular damage to the guinea pigs.

Concerning group 4 (co-administration of caffeinated paracetamol and artesunate), study revealed no significant differences (P>0.05) in the levels of ALT, AST and ALP when compared with the control group. This could be due to the molecular mechanisms of the combined effects of both drugs. Co-administration of caffeinated paracetamol and artesunate could reduce liver damage, maintain liver integrity and cause no hepatotoxicity and hepatocellular damage on the liver enzymes. This observation is in agreement with the work of (*Aronoff et al.,* 2006) in which caffeination of paracetamol results in the reduction of serum enzyme levels and protects the integrity of the liver, and that of (*Taylor and White,* 2004) which suggests that artesunate when administered in normal dosage, cause no hepatocellular damage or hepatotoxicity on the guinea pigs.

Finally when the initial and final weights of the control group (group 1) was obtained, there was a slight increase in the body weight which was not statistically significant (P>0.05). The increased weight may be attributed to the free access of food and water to these guinea pigs and efficient food utilization. However, there was statistically significant differences (p<0.05) in the mean values of the final body weight of group 2, 3 and 4 compared to the mean value in the initial body weight of the guinea pigs. This could be due to the effects of these drugs on the weights of the guinea pigs even when co-administered.

VI. CONCLUSION

In conclusion, the insignificant effects of the administration of artesunate and caffeinated paracetamol drugs on the activities of ALT, AST and ALP levels of the guinea pigs, suggests there were no hepatotoxicity /or hepatocellular damage on the guinea pigs, even with co-administration of both drugs no adverse effects of these drugs on the liver of the guinea pigs were noted. So it suggests that co-administration of these two-drugs at recommended doses have protective roles in the maintenance of liver cells.

VII. RECOMMENDATION

It is advisable that the intake of these drugs be strictly regulated and under the doctor's prescription. Manufacturers of caffeinated paracetamol should regulate the concentration of both its caffeine and paracetamol constituents to limit the possibility of liver damage.

However, not much investigation or information have been documented on the adverse effects of artesunate on the liver since it is the organ of metabolism of drugs and other substances. Further research on this present study is recommended.

ACKNOWLEDGEMENT

We would like to express our immense gratitude and appreciation to Prof. Prince Unekwe, professor of Pharmacology and Therapeutics, Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria, for his scientific inputs. This work was self- funded. We did not receive any financial funding or support from any person or institution.

REFERENCES

[1] Aronoff D.M, Oates J.A, Boutard O, (2006). "New insights into the mechanisms of action of acetaminophen: its clinical pharmacologic characteristics reflects its inhibition of the two prostaglandin H2 Synthases". *Clin. Pharmacol Ther*. **79(**1): 9 – 19.

[2] Allen A.L, (2005). "The diagnosis of acetaminophen toxicosis in a cat". *Canadian Veterinary Journal* **44** (6): 509 – 510.

[3] Baumann T.W, (1997). "Metabolism and Excretion of caffeine during germination of coffee Arabica L". *Plant and cell physiol Journal* **25** (8): 1431 – 36.

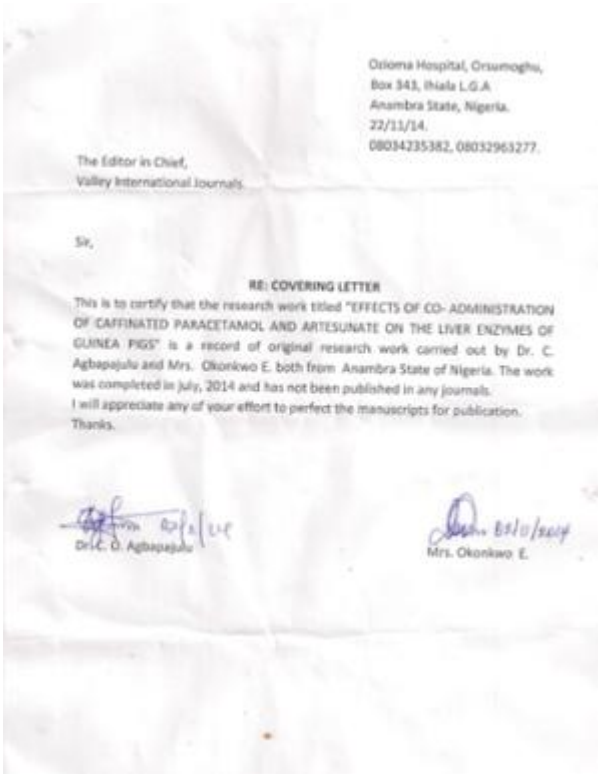
[4] Kummer A.U, (2008) "Caffeine consumption as beverages". *Animal Review of Nutrition medline* **53** (2): 329 – 340.

[5] Sherman K.E, (1999) "Alanine Aminotransferases in clinical practice". *Arch international medicine* **151** (2): 260 – 5.

[6] Lawrence J, Moore E, port L, Danchini M, Counel T, (2009) "Paracetamol as a risk factor for allergic disorders". *The Lancet* **373** (9658): 119 – 120.

[7] Abdin M.Z, Israr M, Rehman R.U, Jain S.K, (2003). "Artemisinin a novel antimalaria drug: Biochemical and molecular approaches for enhanced production". *Planta med.* **69** (4): 289 – 99.

[8] Taylor W.R and white N.J (2004) "Antimalaria drug toxicity". *A review Drug safety* **5** (27): 25 – 61.



Oziona Hospital, Orsumoghu,
Box 343, Ihiala L.G.A
Anambra State, Nigeria.
22/11/14.
08034235382, 08032963277.

The Editor in Chief,
Valley International Journals.

Sir,

RE: COVERING LETTER

This is to certify that the research work titled "EFFECTS OF CO- ADMINISTRATION OF CAFFINATED PARACETAMOL AND ARTESUNATE ON THE LIVER ENZYMES OF GUINEA PIGS" is a record of original research work carried out by Dr. C. Agbapajulu and Mrs. Okonkwo E. both from Anambra State of Nigeria. The work was completed in July, 2014 and has not been published in any journals.
I will appreciate any of your effort to perfect the manuscripts for publication.
Thanks.

Dr. C. Agbapajulu

Mrs. Okonkwo E.