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Synergistic Ingestion of Tramadol, Calabash Chalk (Nzu), Cigarette, Alcohol and Codeine: It's Impact on the Renal and Hepatic Function of Male Humans

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Abstract

The abuse of drugs and substances by youths globally has become a cause for great concern as it does not just lead them to detrimental acts of violence, but also affects the health of the consumers. This study investigated the effect of ingestion of a mixture of tramadol, calabash chalk, cigarette, alcohol and codeine on the renal and hepatic function of male humans. The subjects were young males of age range 18-25 years, 40 of which have been exposed to the mixture for over one year, this group served as the Addict group. The non-addicts group were 40 young males of 18-25 years that have never been exposed to the substances and drugs. Blood samples were collected from respondents into EDTA and plain bottles and analysed in the laboratory for Blood urea nitrogen (BUN), Creatinine, and Blood electrolytes (Sodium (Na^+), Potassium (K^+), Chloride (Cl^-) and Bicarbonate (HCO_3^-), as indicators of renal function, while the hepatic biomarkers were Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total protein (TP), Albumin (ALB), Total Bilirubin (TB) and Conjugated Bilirubin (CB). The results obtained revealed a distinct variation between the addict subjects and the non-addict subjects in all parameters analysed. Na^+ showed a statistical significant difference between the addict subjects and non-addict subjects. The study therefore submitsthat the synergistic intake of tramadol, calabash chalk, cigarette, alcohol and codeine altered the renal and hepatic function of male humans adversely and reduces the haemostatic function of the renal cells.

Keywords: Drug abuse; Substance abuse; Hepatic biomarkers; Renal biomarkers; Blood Electrolytes

Introduction

The intake of drugs in doses not prescribed by the doctor mainly psychoactive, analgesic, and narcotic substances is a threat to the health of young people who engage in this practice. This harm matrix as described by Morgan et al., 2013[1] can be categorised into three: Physical, dependence-related and social. In the United States of America, one in four deaths can be attributed to alcohol, tobacco and illicit or prescription drug use (NIDA, 2020)[2]. Drug abuse is on the increase in Nigeria and the mixture of opioids and several other substances to get a better feeling of 'being high' is highly reported (Quartz Africa, 2018).

Alcoholic beverages are a routine part of the social landscape for many in the population. This is particularly true for those in social environments with high visibility and societal influence, nationally and internationally, where alcohol frequently accompanies socializing. Alcohol is a toxic and psychoactive substance with dependence producing propensities. Alcohol is the leading risk factor for premature mortality and disability among those aged 15 to 49 years, accounting for 10 percent of all deaths in this age group (WHO, 2011)[4]. Abuse of alcohol via excessive intake has been report-

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ed to lead todevelopment of chronic diseases, death, shortening of lives by 30 yearsamongst working-age adults aged 20-40 years[5,6] (Stahre et al., 2014; CDC fact sheet). Alcohol has been found to alter the function of the kidneys, impairing their ability to regulate the composition of fluid and electrolytes in the body.

Calabash chalk also known as the Calabar stone may not be a conventional food but it is consumed virtually by a wide range of people of diverse race or culture. In Nigeria, pregnant and breast feeding mothers were mostly the ones patronizing this product but of recent, the youth (male and female) patronize this product more[7] (Ekong et al., 2008). A one-on-one chat with a seller revealed that "youths purchase this product more and it is lucrative". An addict to it said it makes them high as it gives them the strength and vigour to perform their daily activity especially when taken with other drugs like tramadol and cigarette".Calabash chalk is composed of Aluminium silicate hydroxide from the kaolin clay group with the possible formula Al2Si2O5OH4 (Ekong et al.,2008)[7]. Several study carried out on the product has shown that it contains lead and arsenic which are poisonous substances that can cause death to the consumer (Ekong et al., 2008) [7]. Consumption of this product by pregnant and breast feeding women poses a risk to the mental development of their developing unborn babies and breast feeding infants[8] (Ferguson et al., 2011). Ekong et al., (2008) [7] reported that the non-salted calabash chalk is detrimental to the liver and thus maybe detrimental to health.

Tobacco is a psychoactive material,it is usually rolled into a thin paper usually in a narrow cylindrical shape for smoking[9] (Hoffman and Hoffman, 1997). It is gotten from leaves of tobacco plant. Cigarette can be taken into the body in several ways like smoking, adding its content to food, pipe and at times, its content can be chewed or eaten raw. Cigarette contains several toxic chemicals thus; many manufactured cigarettes have filters on one end that are intended to trap some of the toxic chemicals in cigarette smoke.

Cigarette smoke is both toxic and addictive to not just the smokers but even someone inhaling it, it contains around 7,000 chemicals, many of which are poisonous and over 60 are known to be cancer causing (carcinogenic) (Rodgman and Perfetti, 2009). Fowles and Dybing, (2003)[10] in their study reported that Cigarette smoking harms nearly every organ of the body, causes many diseases, and reduces the health of smokers in general. (Abdel-Rahman El-Zayadi, 2006) reported that lighting a cigarette creates over 4000 harmful chemicals with hazardous adverse effects on almost every organ of the body.

Tramadol is a narcotic analgesic proposed for severe pain sold under several trade names like Ultram, Ultracet, Conzip, etc. (Simon, 2017)[11]. It is approved for the treatment of pain in adults that is severe enough to require an opioid analgesic and for which other treatments do not work or are not tolerated. Tramadol is metabolized through the liver. Over 30% of tramadol is excreted by the kidneys as the unchanged molecule, which means it could lead to toxic blood levels in patients with kidney disease.

The renal and hepatic cells functions in homeostasis and numerous functions such as excretion of waste, metabolism of many substances, hormonal regulation and proper digestion, as well as proper coagulation.

Brian and Jacquelyn, (2005)[12] states that the Liver function tests are blood tests used to help diagnose and monitor liver disease or damage. The tests measure the levels of certain enzymes and proteins in your blood. Some of these tests measure how well the liver is performing its normal functions of producing protein and clearing bilirubin, a blood waste product. Other liver function tests measure enzymes that liver cells release in response to damage or disease.

The harmful effect of alcohol, calabash chalk, cigarette, codeine and tramadol on the body have been reported hence the need to assess the impact of these drugs and substance abuse on the kidney and liver functions when used synergistically.

Materials and Methods

The research design was descriptive and analytical.

Ethical Approval: Ethical approval for the study was obtained from the Rivers State ministry of health, Rivers State health research ethics committee and Rivers State hospital management board, Port Harcourt, Nigeria.

All test and control human subjects for the study duly gave their consent by filling the questionnaire administered to them.

Study population/area: the study involved 80 male humans of 18-25 years resident in Obio/Akpor local government area of Rivers State, Nigeria. They were divided into two batches:
Batch A:20 Addicts and 20 Non-Addicts
Batch B: 20 Addicts and 20 Non-Addicts

Addict group: 40 male humans of age range 18-25 years that were addicts, who regularly ingested a mixture of Alcohol, Calabash chalk, tobacco, codeine and tramadol for over one year. This group was taken as the test group

Exclusion criteria: Addicts and non-addicts who had health issues and comorbidities such as asthma and Human Immuno-Deficiency Virus were excluded.

Non-Addict group: 40 malehumans of age 18-25 years that are non addicts, who did not engage and had never been engaged or exposed to these substances. This group was taken as the control group.

Analysis of Electrolytes, Hepatic and Renal function biomarkers

Five millilitres of blood was collected from the cubital fossa of each respondent and placed in a plain bottle, screened and analysed in the laboratory for estimation of electrolytes, the renal and hepatic function biomarkers. The electrolytes assayed include: Sodium (Na^+), Potassium (K^+), Chloride (Cl^-) and Bicarbonate (HCO_3^-). The renal function biomarkers include: Blood Urea Nitrogen (BUN) and Creatinine (Cr). The hepatic function biomarkers includes: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Total protein (TP), Albumin (ALB), Total Bilirubin (TB) and Conjugated Bilirubin (CB) using standard assay kits: "Randox" reagent kit (Randox Laboratories Ltd. London, 140 London Wall, EC2Y 5DN)

Statistical Analysis: All data generated were analysed using one way Analysis of Variance (ANOVA) with the aid of Statistical Package for Social Sciences (SPSS) version 20 running on Windows PC. Data for each parameter were expressed as mean value ± standard deviation. The significant differences between the test means and control means were determined at $p<0.05$ confidence level.

Result

Theeffect of synergistic intake of alcohol, calabash chalk, tobacco, codeine and tramadol on the renal and hepatic function biomarkers was assessed. The result of the analysis revealed an adversely marked alteration in the concentration of the biomarkers for both batch A and B as shown in tables 1, 2, 3 and 4.

Table 1: Effect of synergistic intake of alcohol, calabash chalk, tobacco, codeine and tramadol on the renal function of Batch A subjects

Electrolytes (mmol/L)	Addicts (n=20)	Non-addicts (n=20)
Na^+	145.250^{b}±1.71	132.400^{a} ±8.17
K^+	3.825^{a} ±0.22	3.560^{a} ±0.74
HCO_3^-	25.500^{a} ±3.00	26.000^{a} ±3.16
Cl^-	68.500^{a} ±4.44	67.600^{a} ±6.19
Renal function biomarkers		
BUN(mmol/L)	4.600^{a} ±2.52	3.820^{a} ±0.51
Creatinine(µmol/L)	89.250^{a} ±39.61	73.400^{a} ±10.48

•Values are expressed as mean ± standard deviation.
•Values with different superscripts show significant difference at P<0.05

Table 2: Effect of synergistic intake of alcohol, calabash chalk, tobacco, codeine and tramadol on the renal function of Batch B subjects

Electrolytes(mmol/L)	Addicts(n=20)	Non-addicts(n=20)
Na^+	145.500^{b} ±1.52	128.400^{a} ±3.85
K^+	3.750^{a} ±0.61	3.260^{a} ±0.34
HCO_3^-	27.000^{a} ±2.76	24.800^{a} ±2.28
Cl^-	70.833^{a} ±4.49	65.400^{a} ±5.27
Renal function biomarkers		
BUN (mmol/L)	5.150^{a} ±2.42	3.080^{a} ±0.58
Creatinine(µmol/L)	106.500^{a} ±36.21	68.200^{a} ±7.85

•Values are expressed as mean ± standard deviation.
•Values with different superscripts show significant difference at P<0.05

Table 3: Effect of synergistic intake of alcohol, calabash chalk, tobacco, codeine and tramadol on the Hepatic function biomarkers of Batch A subjects

Biomarkers	Addicts (n=20)	Non-addicts (n=20)
AST(U/L)	9.80^{b}±2.39	6.40^{ab} ±1.52
ALT(U/L)	6.40^{a} ±2.61	5.60^{a} ±1.67
ALP(U/L)	35.00^{bc} ±3.39	24.80^{a} ±3.96
TP(g/L)	62.00^{a} ±3.39	73.80^{c} ±3.90
ALB(g/L)	33.60^{a} ±3.05	42.40^{b} ±1.82
TB(µmol/L)	14.10^{b} ±1.17	8.20^{a} ±1.43
CB(µmol/L)	8.8^{b} ±1.15	4.02^{a}±0.67

•Values are expressed as mean ± standard deviation.
•Values with different superscripts show significant difference at P<0.05

Table 4: Effect of synergistic intake of alcohol, calabash chalk, tobacco, codeine and tramadol on the Hepatic function biomarkers of Batch B subjects

Biomarkers	Addicts (n=20)	Non-addicts (n=20)
AST(U/L)	6.80^{ab} ±2.78	5.60^{a} ±1.52
ALT(U/L)	7.20^{a} ±3.35	4.80^{a} ±1.10
ALP(U/L)	37.40^{c} ±7.64	28.00^{ab} ±3.39
TP(g/L)	64.40^{ab} ±7.30	71.80^{bc} ±2.86
ALB(g/L)	36.20^{a} ±3.90	42.60^{b} ±2.51
TB(µmol/L)	15.50^{b} ±2.53	10.10^{a} ±2.43
CB(µmol/L)	9.36^{b}±2.56	5.46^{a} ±1.6

•Values are expressed as mean ± standard deviation.
•Values with different superscripts show significant difference difference at P<0.05

Discussion

The abuse of drugs is a threat to mankind and the environment at large thus, a need for urgent remedy as the abuse of drugs is on the increase daily despite government warnings and laws Brian and Jacquelyn (2005)[12]. Thisstudy evaluated the impact of synergistic intakeof tramadol, calabash chalk, cigarette, alcohol and codeine in the proper functioning of the renal and hepatic cells of male humans. The result for the blood electrolytes (Na^+, K^+, HCO_3^- and Cl^-) as shown in table 1 revealed anincrease and statistical significant difference in the Na^+ concentration of the addicts when compared to the non-addicts for both batch A and batch B. This hypernatremia seen in both batch A and B of addicts suggests an imbalance in water regulation in the kidneys. Alcohol intake has been seen to cause hypernatremia by inhibiting the action of vasopressin which causes water reabsorption from the kidney. Alcohol also directly influences the kidney's handling of sodium and other electrolytes potentially resulting in hypernatremia (Murray, 1997)[13]. A decreasing difference was observed in the concentrations of K^+, and Cl^-, however, the decrease was not significant at P<0.05 when compared to the non-addict in the both batches. HCO_3^- level was observed to decrease in the addict when compared to the non-addict group in batch A, but was reversed in Batch B. The Blood urea nitrogen (BUN) concentration of the addicts in batch A and B were seen to increase when compared to the non-addicts. BUN excretion

by the kidney has been reported to be reduced in renal diseases (Weiner et al., 2015)[14]. Creatinine concentrations were also seen to increase for the addicts when compared to the non-addict concentration, however, not statistically significant. High creatinine levels have been reported to be associated with renal function impairment. The above result implies that the addicts were vulnerable to an impairment of renal function as revealed in the data in comparison with the non addicts. This result submits with the findings of (Bundy et al., 2018; Fan et al., 2019) [15,16] that consumption of drugs in doses not prescribed can alter the function of the kidneys negatively.

The biomarkers tested for liver disease include Alanine transferase (ALT) and Aspartate transaminase (AST) to detect possible hepatocellular damage, Alkaline Phosphatase (ALP) for cholestasis, Total Protein(TP) and Albumin (ALB) for synthetic function and Total bilirubin (TB) and conjugated bilirubin (CB) for excretory function (Mayne, 1994)[17]. In the hepatic analysis, the data obtained after subjecting the result obtained from the analysis to a one way analysis of variance at 95% confidence level showed significant difference increasingly at $P<0.05$ in the addict for all comparison to the non-addict group for both batch A and B for AST, ALP, TP, ALB, TB, and CB as observed in table 3 and 4. ALT concentration however, was also seen to increase in the addict group in comparison to the non-addict group for both batch A and B.The increase in AST, ALT and bilirubin is in keeping with the study done by Agarwal et al., 2015[17] where these enzymes were assessed in alcoholics and found to be increased compared to non-consumers. This suggests on-going liver pathology in the addict group. Alatalo et al., 2009[19] in their study also reported an increased concentration in hepatic function biomarkers of heavy drinkers, and their report is in consonance with the data obtained from this study. The intake of tramadol may have also resulted in the increase of some of the biomarkers as it has been seen that serum aminotransferase levels can be elevated in a small proportion of patients receiving tramadol particularly with high doses (NIDDKD, 2012)[20]. The data obtained in this study also shows a statistically significant decrease in Total Protein and Albumin suggesting that the synthetic function of the liver may have been hampered by the synergistic intake of the substances involved. Our study also showed a significant increase in Total bilirubin and Conjugated bilirubin which suggests impairment on the excretory function of the liver. These are in keeping with the study by Ebuehi and Asonye, (2007)[21] where Total Protein and albumin levels as well as bilirubin levels were impaired in alcoholics compared to non-alcoholics.

These results imply that in the future, these addicts are likely to come down with renal and liver diseases which may be life threatening.

Conclusion

The data obtained from this study for the renal and hepatic function submits that the synergistic intake of mixture of tramadol, calabash chalk, cigarette, alcohol and codeine may lead to renal and hepatic dysfunction which could later lead to death. This study was rather limited in that we did not have the exact concentrations or quantity of the substances taken over the said period of time. We also recommend that further studies should assay blood samples for gamma-glutamy ltransferase in order to check for acute alcoholic hepatitis.

Recommendation

The authors recommend a proper sensitization of the masses on the negative effect of these substances on mankind in addition to stringent regulation on the use of tramadol and codeine for Socrates said "an unexamined life is not worth living".

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