Antibiotics Administration and its Possible Liver Damage

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Abstract

The effect of antibiotics on two liver enzymes – serum alanine aminotransferase (ALT) also known as glutamic-pyruvic transaminase (SGPT) and serum alkaline phosphatase (ALP) – was studied in a population of adults in Nsukka, Enugu state Nigeria. Standard clinical methods were used for the assays. The results show statistically significant increase ($p<0.05$) in the levels of both enzymes (which are markers of hepatocellular integrity) in the subjects who took antibiotics when compared to those who did not consume antibiotics. There were no significant differences ($p>0.05$) between the means of both ALT and ALP for the different sexes. There were however, statistically significant differences ($p<0.01$) in the means of both ALT and ALP for the number of different antibiotics taken and the duration of antibiotics' intake. A very strong positive correlation was seen between ALT and ALP ($r = +0.767$, $p<0.001$) and between each of the enzymes and the number of different antibiotics taken irrespective of the duration the antibiotics were taken ($r = +0.898$, $p <0.01$ for ALT; $r = +0.657$, $p<0.01$ for ALP). Also, there was a strong positive correlation between ALT and ALP and the duration of intake of antibiotics irrespective of the number of different antibiotics taken ($r = +0.795$, $p<0.001$ for ALT; $r = +0.713$, $p <0.001$ for ALP). Both enzymes were weakly, and negatively correlated with the age of the subjects ($r = -0.282$, $p<0.01$ for ALT; $r = -0.230$, $p<0.05$) for ALP). The study indicts antibiotics in the causation of hepatic damage and calls for caution in the prescription and use of antibiotics by health practitioners and the public.

Keywords: Antibiotics, Liver, Serum alanine aminotransferase, Serum alkaline phosphatase

Introduction

Antibiotics originally referred to only organic substances produced by bacteria and molds, which are toxic to other organisms. However, the term is now loosely used to include synthetic and semi-synthetic organic compounds that are used to inhibit the growth of, or kill, pathogenic organisms (Brock and Madigan, 1988). The liver contains enzymes that are continuously employed in the alteration and destruction of not just ingested xenobiotics but also toxins that are produced by the body through normal daily living. When tissue damage occurs, cellular enzymes are released into the serum and the elevation of certain enzymes in the serum is often associated to tissue or organ damage or dysfunction. In the same manner, damage to hepatocytes results in the influx of liver enzymes, chiefly aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma glutamyl transpeptidase, into the serum (ASCP, 2003). The rate at which antibiotics are taken for illnesses ranging from stomach upset to other more serious illnesses, often without appropriate diagnosis and in self medication is increasing drastically. The sale of antibiotics by patent medicine dealers over the counter has contributed immensely in fuelling this problem. It is also becoming common practice for people to use more than one antibiotic at a time, over a period of days, to cure their ailments. Cases of prescription of antibiotics by medical personnel without any thought of the possible side effects of the drugs are also rampant. It has therefore become imperative to investigate the effect antibiotics have on the liver, by monitoring the levels of the enzymes ALT and ALP, in the serum of individuals on antibiotics. This we hope would provide information in the direction of the appropriate use of the agents by highlighting the deleterious effects of the antibiotics.

Materials and Methods

Subjects: Adult human beings, of ages between twenty and fifty eight, totaling ninety in number and residing in Nsukka, Enugu state Nigeria were recruited for the study. Of this number, forty subjects (nineteen males and twenty one females) who had not taken any antibiotic drug for at least one year prior to sampling served as control subjects. A total of fifty subjects (twenty males and thirty females) who had stitched 'minor' wounds, and were placed on antibiotics to prevent microbial infection of their wounds were taken as test subjects. All test subjects were sourced from hospitals in the Nsukka metropolis whose management approved the study. Only those subjects whose hospital records showed they were not suffering from any other known ailments, but who had taken antibiotics for at least two days were approached and subsequently recruited for the study. Female subjects who had overt signs of pregnancy, or who reported being pregnant, were excluded from the study. All the recruited subjects freely volunteered to be part of the study and each one of them gave an informed verbal consent.

Samples: Venous blood (4ml) was collected from each subject using disposable syringes.

Table 1: Summary of results from test and control subjects

	Mean Age ± SD (Years)	Mean Nọ of Different Antibiotics Taken ± SD	Mean Nọ of Days of Intake ± SD	Mean ALT ± SD (U/L)	Mean ALP ± SD (U/L)
Test Subjects	32.5 ± 9.61	1.88 ± 0.90	4.50 ± 2.21	20.38 ± 2.82	259.00 ± 30.29
Females (n =30)	33.07 ± 9.48	1.97 ± 0.96	4.50 v 2.40	20.53 ± 2.87	260.82 ± 30.61
Males (n=20)	31.16 ± 9.79	1.75 ± 0.79	4.50 ± 1.93	20.15 ± 2.81	256.26 ± 30.36
Control subjects	38.5 ± 9.09	0.00 ±0.00	0.00 ±0.00	8.88 ± 2.15	159.11 ± 32.94
Females (n=21)	39.48 ± 8.89	0.00 ± 0.00	0.00 ± 0.00	8.86 ± 2.37	159.42 ± 33.09
Males (n=19)	37.32 ± 9.42	0.00 ± 0.00	0.00 ± 0.00	8.89 ± 1.94	158.77 ± 33.68
Total (n=90)	35.16 ± 9.79	1.15 ± 0.12	2.50 ± 2.78	15.27 ± 6.28	214.60 ± 58.92

Nọ stands for number, SD for standard deviation and n for number of subjects.

The samples were transferred to anti-coagulant-free sample containers and left to clot. Thereafter, they were centrifuged at 2500g for 5 minutes to separate the cells from the serum. The serum was pipetted (2ml) into fresh containers and stored in a freezer at -10°C until used.

Methods for assays: Serum alanine aminotransferase was assayed by the method of Reitman and Frankel (1957) while serum alkaline phosphatase was assayed by the method of Rec (1972). Both were done using commercially available test kits (Randox Laboratories Ltd, Crumlin, Co., United Kingdom).

Statistical analysis: Differences between means were separated using the one way analysis of variance (ANOVA) test, while the Pearson's correlation coefficients were calculated to assess association between variables. Both tests were done with the aid of the SPSS for windows version 11.0 package (SPSS Inc., Chicago, IL).

Results

The average ages for the test and control subjects were 32.5 and 38.5 years respectively. The difference in the mean ages of the subjects in both groups irrespective of sex were not statistically significant ($p>0.05$). However, there was a statistically significant difference ($p<0.05$) in the mean ages of the females in the test and control groups. On the average, each of the test subjects took approximately two different antibiotics for between four and five days. The mean ALT and ALP values were 8.88 ± 2.15U/L and 159.11 ± 32.94U/L respectively for the control subjects, while the mean values for both enzymes in the test category were 20.38 ± 2.82U/L and 259.00 ± 30.29U/L respectively (Table 1).

The levels of the two liver enzymes studied were not statistically different ($p>0.05$) for both sexes in the test and control groups (Table 1). However, the level of the enzymes remained conspicuously higher in the test subjects when compared to the control group. A test of correlations also revealed that there was no significant correlation between the two enzymes and the sex of the subjects.

Figure 1 reveals that the levels of the studied enzymes oscillated around the same values for the three age ranges, both in the test group and in the control group. The levels of the enzymes for the control groups however remained clearly lower than those of the test groups. There was no significant difference ($p>0.05$) in the mean values of ALT and AST for the different age ranges. There were weak negative correlations between age of subjects and number of antibiotics taken ($r = -0.245$, $p<0.05$), duration of antibiotic intake ($r = -0.257$, $p<0.05$), levels of ALT ($r = -0.282$, $p<0.01$) and ALP ($r = -0.23$, $p<0.05$).

The level of ALT for the test group increased step-wise as the number of antibiotics taken increased (Fig. 2A). The trend noticed for ALP is different as it dropped after those who took two antibiotics. However, regardless of the number of antibiotics taken, the levels of both enzymes remained markedly higher than those of the control group. There were significant differences ($p<0.05$) in the mean ALP and ALT values of the groups that took different numbers of antibiotics. Strong positive correlations were noticed between the enzymes and the number of antibiotics taken ($r = +0.898$, $p<0.001$ for ALT, and $r = +0.657$, $p<0.01$ for ALP).

Figure 2B shows the level of the liver enzymes as the number of days of antibiotic intake increased. From the figure, it is seen that there was a small but steady rise in the level of ALT of the subjects as the number of days the antibiotics were taken increased. For ALP, the increase appears more marked, but dropped at 6-8 days, only to peak at 8 or more days. In any case, the levels of the enzymes were lower by 50% or more in the control group when compared to even those who took antibiotics for only 2-3 days. The means of ALT and ALP were significantly ($p<0.01$ in each case) different with respect to the number of days the antibiotics were taken. There were strong positive correlations between the duration of antibiotic intake and both the levels of ALT ($r = +0.795$, $p<0.001$) and ALP ($r = +0.713$, $p<0.001$). In all cases, the levels of serum alanine aminotransferase highly correlated positively with the levels of alkaline phosphatase in the subjects ($r = +0.767$, $p<0.001$).

Discussion

The liver serves many metabolic functions, yet quantitative markers for liver function are not available in everyday practice. Estimation of liver injury is therefore indirect, and recognizing the severity of hepatic injury can also be problematic (King and Perry, 2001). Although alanine aminotransferase and alkaline phosphatase are present in tissues around the body, their elevation (particularly in combination) is most often associated with liver injury or disease. Of all known liver enzymes, ALT is known to be highly liver-

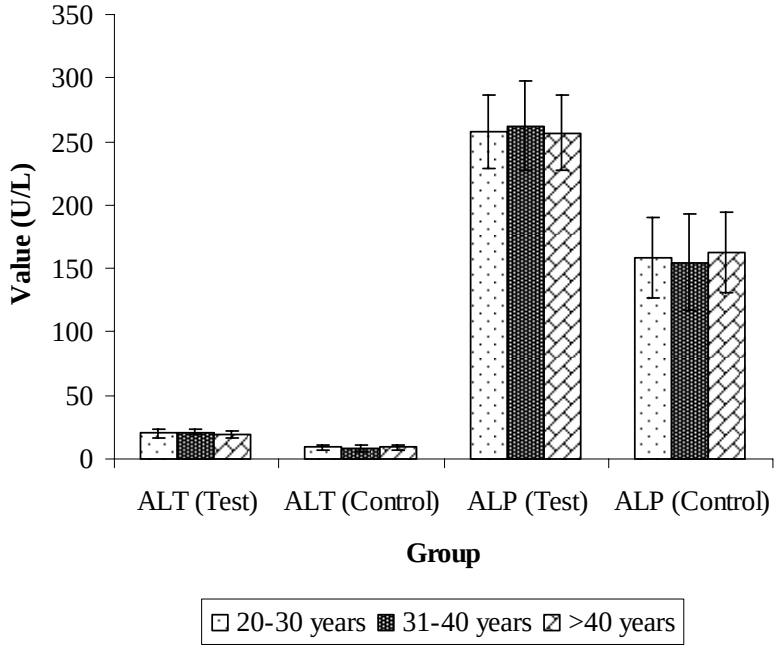

Fig. 1: Levels of ALT and ALP in the subjects of different age ranges, irrespective of sex

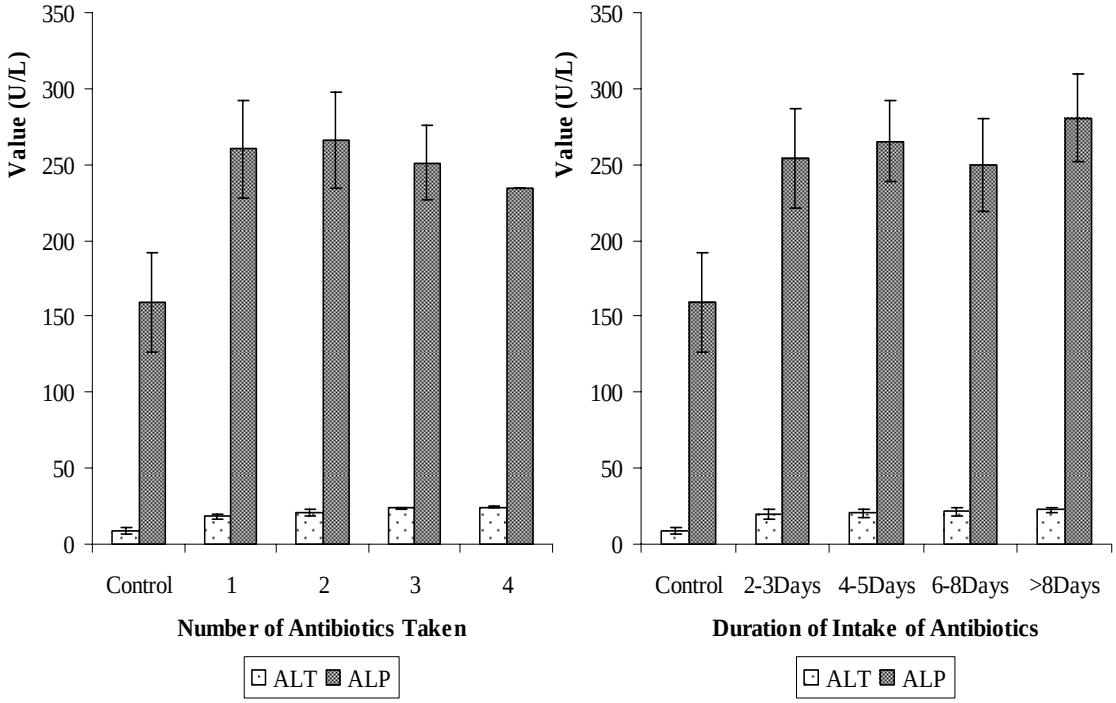

Fig. 2: Levels of ALT and ALP in the subjects who took different antibiotics together, irrespective of duration (A), and for different numbers of days, irrespective of the number of different antibiotics taken (B).

specific, while ALP elevation in the presence of an elevation of any of the transaminases, indicates bile duct obstruction especially within the liver (ASCP, 2003). The increase in the liver enzymes studied (in the test subjects) may therefore show the level of destruction of hepatocytes or alteration in hepatocytes' functions. Burling (2006) reported that mild or moderate elevations in ALT is a more specific enzyme marker of hepatocellular damage, but is causally nonspecific and may be due to a wide range of liver diseases. He also reported that the level of ALP is elevated in a number of disorders that affect the drainage of bile such as drug-induced hepatitis or by having the flow of bile blocked in smaller channels within the liver. Bhalli *et al*. (2006) reported elevations in the levels of ALT and AST in workers exposed to pesticides in Pakistan, and attributed it to genotoxicity. The present study shows that the toxicity of antibiotics may be responsible for the observed elevations in ALT and ALP. Although, many pharmaceuticals can cause liver injury, most hepatotoxic drug reactions are idiosyncratic, due to immunologic mechanisms or variations in host response (Lee, 1995). Huet *et al.* (1997) support this position. These hepatotoxic drug reactions are not typically dose-dependent. Less common are dose-dependent, predictable toxic effects of a medication or its metabolites (King and Perry, 2001). Our results however, show a dose-dependent increase in the level of these enzymes with respect to the number of antibiotics taken and the number of days for which the antibiotics were taken. The subjects took fewer antibiotics for fewer days, with advancing age. This may be due to a deliberate effort by the hospitals to reduce the number and duration of antibiotics given to people as they age. This may also explain the negative correlation between age and ALT and ALP. Obi *et al.* (2003) showed an increase in these enzymes with age. The positive correlation between ALT, ALP and the number of different antibiotics taken and duration of intake shows that antibiotics may be at the centre of the observed increase in the levels of the studied liver enzymes. Sex however was not found to contribute to this observed increase in the liver enzymes. ASCP (2003) reports that males may have slightly higher ALP values than females (provided the females are not pregnant). However, the results obtained from the females in our study were not significantly different when compared to the males. We conclude that the number of antibiotics taken and the duration of intake are the most likely causes of hepatocellular damage in the studied population. Caution should be employed in the use of antibiotics especially when they are not prescribed by trained medical personnel.

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