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Effects of Acute Migraine Therapy on Hepatic and Renal Functions

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Research Article

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Abstract

This study is aimed at evaluating the effects of sumatriptan and Cafergot® (Dihydroergotamine + caffeine) tablet on the hepatic and renal functions in acute migraine patients so as to guide physicians in the rational management of migraine in clinical practice. Seventy three consecutive adult migraineurs that attended the Neurology Clinic of the Department of Medicine, University of Maiduguri Teaching Hospital from May, 2009 to December, 2010 and met the inclusion criteria were evaluated with their consents. The success of acute antimigraine therapy was prospectively studied at which the hepatic and renal functions were assessed. Acute therapy with sumatriptan 50 mg (N=30) caused a significant increase in the levels of alanine aminotransferase (ALT), bicarbonate (HCO_3^-), creatinine, total protein, aspartate aminotransferase (AST), chloride, urea, total bilirubin, conjugated bilirubin, alkaline phosphatase and potassium (K^+) ($p<0.05$). Similarly, the levels of albumin, chloride, creatinine, total bilirubin, ALT, K^+, conjugated bilirubin, alkaline phosphatase, AST, HCO_3^- and urea were able to increased significantly due to acute therapy with sumatriptan 100 mg ($p<0.05$). There was a statistical significant difference in the levels of AST, chloride, total bilirubin, total protein, albumin, alkaline phosphatase, ALT, urea and conjugated bilirubin ($p<0.05$) among the 9 patients that took Cafergot® 1 mg. Cafergot® 2 mg (N=11) caused a significant increase in the levels of total protein, K^+, urea, total bilirubin, conjugated bilirubin, AST, HCO_3^- and chloride ($p<0.05$). The effects of Cafergot® and sumatriptan on hepatic and renal functions were not dose dependent and did not differ significantly. The impact of sumatriptan and Cafergot® therapy on the hepatic and renal functions showed a significant increase in most of the biochemical analytes and enzymes (except sodium) among the migraineurs studied.

Keywords: *Acute migraine, therapy, hepatic and renal function*

Introduction

Migraine is a highly prevalent headache disorder that has a substantial impact on the individual and society. A study in humans has demonstrated that concentrations of calcitonin gene-related peptide, a substance that increases vascular permeability and promotes plasma protein extravasation [1], are elevated during a migraine and return to normal as the headache is relieved by sumatriptan [2]. There are numerous options for acute migraine relief and patients vary in their responses to different medications [3]. Ergot derivatives (e.g. Dihydroergotamine) and triptans (e.g. sumatriptan) were found to be effective antimigraine agents in clinical practice [4, 5, 6, 7]. Their interaction with 5-$HT_{1B/1D}$ receptor could account for their antimigraine action [8]. They stimulate 5-$HT_{1B/1D}$ receptors in the intracranial blood vessels and nerves of the trigeminal system which result in constriction of cranial vessels and inhibition of pro-inflammatory neuropeptide release [6].

Approximately 80% of a sumatriptan dose is metabolized by the liver [1, 9, 10, 11] and the major metabolite is an inactive indole acetic acid derivative [12]. In vitro studies with human hepatic microsomes indicate that sumatriptan is metabolized by monoamine oxidase (MAO), primarily the A isoenzyme (MAO-A) [13]. Sumatriptan is eliminated via active renal tubular secretion [1, 9, 10], following hepatic metabolism. The effects of renal function impairment on clearance of sumatriptan have not been studied [9, 12]. Hepatic function impairment should be more likely than renal function impairment to produce clinically significant elevations in the bioavailability of orally administered sumatriptan [1, 9, 13].

No evidence of mutagenicity, tumorgenicity, teratogenicity or embryolethality was found in a variety of *in vitro* and *in vivo* studies [12, 13].

Metabolism of these drugs by the liver and their subsequent excretion by the kidneys may not be without side effects in this environment as disturbances of renal function test (RFT) and liver function test (LFT) have been reported [14]; with caution on the use of sumatriptan in patients with impaired hepatic or renal functions [15, 16, 17, 18]. To the best of our knowledge no study was done in this environment to evaluate the effects of these drugs on liver and kidneys. Therefore, the study aims at evaluating the effects of sumatriptan and Cafergot® on liver and renal functions in Maiduguri, Nigeria.

Methodology

From May, 2009 to December, 2010, seventy three (73) consecutive adult migraine patients that attended the Neurology Clinic of the Department of Medicine, University of Maiduguri Teaching Hospital (UMTH), Maiduguri were prospectively studied with their consents. Pregnant women, patients with clinical evidence of an organic disease known to cause migraine and those that have a socioeconomic factor (culture and poverty) were excluded. Personal interviews using a structured questionnaire were conducted individually with the 73 patients. The socio-demographic profile of each patient (age, sex, educational background, occupation, marital status, use of alcohol and smoking behavior), clinical presentation, aggravating/relieving factors and history of drug use (within three months) were obtained. In addition, haematological, immunological and biochemical analysis were done on every study subject to exclude other organic disease known to cause migraine. Those patients that did not meet the inclusion criteria were given analgesics and were not enrolled for the study. The study was approved by the Research and Ethics committee of UMTH.

Sample size determination and sampling technique

The minimum sample size for this study was determined based on the prevalence reported in the literature [19] using the Taylor's formula [20] at which 73 consecutive patients with migraine that satisfied the inclusion criteria were enrolled for the study.

Drug treatment and evaluation of hepatic and renal function

Fifty three (53) and twenty (20) patients enrolled in this study were given sumatriptan and Cafergot® tablets respectively. Thirty (30) patients were given 50mg of sumatriptan, while the remaining 23 received 100mg of sumatriptan. On the other hand, 9 patients were given 1mg of Cafergot® and 11 patients took 2 mg of Cafergot®. Liver function test (LFT) and renal function test (RFT) were performed on each study patient before (immediately) and two weeks after the acute therapy. Five millilitres (5 ml) of blood was acquired aseptically from cubital vein without haemostasis immediately from all the enrolled patients before the acute therapy was given and these were used for the analysis. This was also repeated two weeks after acute therapy with sumatriptan or Cafergot®. Total bilirubin, conjugated bilirubin, total protein, albumin, alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Table 5) were used to assess the effect of sumatriptan and Cafergot® on the liver function. Similarly, the effect of these drugs on the kidney was assessed considering levels of bicarbonate (HCO_3^-), chloride (Cl^-), potassium (K^+), sodium (Na^+), urea and creatinine.

Total bilirubin (Spectrophotometric method): A sample blank was prepared by pipetting 0.1, 1 and 0.1 ml of sulphanilic acid, caffeine and serum sample respectively into a test tube. This was mixed and allowed to stand for 10 minutes (mins) at 25^{o}C in a water bath. Then 1 ml of tartrate was added to the mixture which was mixed and allowed to stand for 20 mins at 25^{o}C. Similarly, the sample was also prepared by pipetting 0.1 ml of sulphanilic acid, 0.5 ml of caffeine, 0.1 ml of serum sample and 1 drop of sodium nitrite was added into a test tube. This was mixed and allowed to stand for 10 mins at 25^{o}C in a water bath. Then 0.5 ml of tartrate was added to the mixture which was mixed and allowed to stand for 10 mins at 25^{o}C. The absorbance of the sample was read against the sample blank at wavelength of 578 nm directly from spectrophotometer (Vital Scientific 5-5773). The UMTH reference value for total bilirubin is 1.7 – 17.1 µmol/L.

Conjugated bilirubin (Spectrophotometric method): A sample blank was prepared by pipetting 0.1, 2 and 0.1 ml of sulphanilic acid, sodium chloride and serum sample respectively into a test tube. This was mixed and allowed to stand for exactly 5 mins at 25^{o}C in a water bath. Similarly, the sample was also prepared by pipetting 0.1 ml of sulphanilic acid, 1 ml of sodium chloride, 0.1 ml of serum sample and 1 drop of sodium nitrite into a test tube. This was mixed and allowed to stand for 5 mins at 25^{o}C in a water bath. The absorbance of the sample was read against the sample blank at wavelength of 546 nm directly from spectrophotometer (vital scientific 5-5773). The UMTH reference value for conjugated bilirubin is 1.7 – 8.5 µmol/L.

Total protein (Biurette method): One milliliter of biurette reagent (sodium tartrate, potassium tartrate, copper sulphate and potassium iodide) and 0.02 ml (20 µL) of serum sample was mixed in a test tube and allowed to stand for 10 mins at room temperature. The absorbance

of the prepared sample (mixture) and that of the standard was measured at 540 nm wavelength using spectrophotometer (vital scientific 5-5773). The concentration of total protein in g/L was calculated as the absorbance of sample divided by the absorbance of standard multiply by the concentration of the standard. The UMTH reference value for total protein is 58 – 80 g/L.

Albumin (Spectrophotometric method): A reagent blank was prepared by pipetting 0.01 ml (10 µL) of distilled water and 1 ml of Bromocresol green (BCG) reagent into a test tube. Standard was also prepared by pipetting 0.01 ml of standard and 1 ml of BCG reagent into a test tube. Finally, the sample was prepared by pipetting 0.01 ml of serum sample and 1 ml of BCG reagent into a test tube. This was mixed and incubated for 5 mins at 25^{o}C in a water bath. The absorbance of the sample and the standard against the reagent blank was read from spectrophotometer (Beckman coulter DU^{R} 520). The concentration of albumin in g/L was calculated as the absorbance of sample divided by the absorbance of standard multiply by the concentration of the standard. The UMTH reference value for albumin is 35 – 50 g/L.

Alkaline Phosphatase (Spectrophotometric method): A sample was prepared by pipetting 1 ml of deionized water and one drop of substrate into a test tube. This was mixed and incubated at 37^{o}C for 5 mins. Zero point one milliliter (0.1 ml) of the sample was added into the above test tube, mixed and incubated in a water bath at 37^{o}C for 20 mins. Five milliliters of the colour developer was then added. Similarly, standard was also prepared by pipetting 1 ml of deionized water and one drop of substrate into a test tube. This was mixed and incubated at 37^{o}C for 5 mins. Then 0.1 ml (100 µL) of alkaline phosphatase standard was added, mixed and incubated at 37^{o}C for 20 mins. Five milliliters of the colour developer was then added. The optical density of the sample and that of the standard against the blank (deionized water) was read from spectrophotometer (Beckman Coulter DU^{R} 520). The concentration of alkaline phosphatase in U/L was calculated as the optical density of sample divided by the optical density of standard multiply by the concentration of the standard [21, 22, 23]. The UMTH reference value for alkaline phosphatase in adults is 60 – 170 U/L.

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT (Spectrophotometric method): A reagent blank was prepared by pipetting 0.5 ml (500 µL) of buffer (AST buffer is different from ALT buffer) and 0.1 ml of deionized water into a test tube. This was mixed and incubated at 37^{o}C for 30 mins. Zero point five millilitre (0.5 ml) of 2, 4-dinitrophenyl hydrazine were added to the mixture which was incubated at 20^{o}C – 25^{o}C for 20 mins. After which 5 ml of sodium hydroxide was added and mixed. Sample was also prepared by pipetting 0.1 ml of serum sample and 0.5 ml of buffer into a test tube. This was mixed and incubated at 37^{o}C for 30 mins. Then 0.5 ml of 2, 4 – dinitrophenylhydrazine was added to the mixture which was incubated at 20^{o}C - 25^{o}C for 20 mins. After which 5 ml of sodium hydroxide was added and mixed. The absorbance of the sample against the reagent blank was read after 5 mins at 546 nm using spectrophotometer (vital scientific 5-5773). The result obtained was compared with the activity of AST and ALT in the serum from the standard table (Table 5) [24, 25]. The UMTH reference value for AST and ALT is≤ 12 U/L and ≤ 12 U/L respectively.

Bicarbonate (Titrimetry Method): Two milliliters of deionized water was pipetted into a universal container and a drop of methyl red (indicator) was added. One hundred microlitres of serum sample was added to the container and a yellow colouration was observed. One milliliter of 0.01N Hydrochloric acid (HCl) was also added and a red colouration was observed. This was titrated by 0.01N NaOH until the red colouration disappeared. The excess NaOH left in the titrating pipette is equivalent to the concentration of HCO_3^- present in the body. The UMTH reference value for HCO_3^- is 20 – 30 mmol/L.

Chloride (Titrimetry Method): One point eight (1.8) milliliters of deionized water was pipetted into a universal container and 2 ml of serum sample was added then 3 drops of diphenyl carbazone indicator was added. This was mixed and then titrated from 2 ml pipette with mercuric nitrate until the pale purple colour appears. The value in the test tube is read (i.e the used volume). The UMTH reference value for Cl^- is 95 – 110 mmol/L.

Sodium and Potassium (Flame Photometry Method): Test sample was prepared by pipetting 10 ml of deionized water and 100 µL of serum sample into a universal bottle. The standard sample was also prepared by pipetting 10 ml of deionized water and 100 µL of working standard. Finally a blank sample was prepared containing only 10 ml of deionized water. All the three samples above were mixed thoroughly and were used for the determination of Na^+ and K^+. For Na^+ (590 nm); the sodium light filter was inserted into the universal bottle above and the flame photometre (CLH, Essex England) was switched on. The cooking gas supply was turn on and the flame was ignited while the air supply was on.

The gas was adjusted smoothly to obtain optimum discrete cone of blue flame. The flame photometre was adjusted to zero mark with deionized distilled water and the reading was set to X using the standard solution. This process was repeated several times. The test is read, checking the standard after 5 tests. For K^+ (770 nm); the potassium light filter was inserted in place of sodium and the whole process was continued as for sodium above. The UMTH reference value for Na^+ and K^+ are 135.0 – 145.0 mmol/L and 3.0 – 5.0 mmol/L respectively.

Urea: Test sample was prepared by pipetting 1 ml of distilled water, 1 ml of working colour reagent (thiosemicarbazide), 1 ml of mixed acid reagent (ferric chloride) and 0.01(10µL) of serum sample into a test tube. The standard sample was also prepared by pipetting 1 ml of distilled water, 1 ml of working colour reagent (thiosemicarbazide), 1 ml of mixed acid reagent (ferric chloride) and 0.01 ml (10 µL) of urea standard solution. Finally a blank sample was prepared containing 1 ml of distilled water, 1 ml of working colour reagent (thiosemicarbazide) and 1 ml of mixed acid reagent (ferric chloride). All the three samples above were mixed thoroughly and were incubated at 100^{o}C for 20 mins in boiling water bath. This was allowed to cool and read using spectrophotometer (Beckman Coulter DU^{R} 520) at 540 nm. The concentration of urea was calculated as the absorbance of sample divided by the absorbance of the standard multiply by the concentration of the standard. The UMTH reference value for urea is 2.5 – 5.8 mmol/L.

Creatinine (Jaffes Reaction): The procedure for determination of serum creatinine is divided into 2 stages. The 1st stage (deproteinization) involves preparation of blank, standard and test samples before centrifugation. The blank sample was prepared by pipetting 1 ml of deionized water, 0.5 ml of 10% sodium tungstate and 0.5 ml of 0.33N H_2SO_4 into a test tube. The standard sample was also prepared by pipetting 0.5 ml of deionized water, 0.5 ml of standard creatinine solution, 0.5ml of 10% sodium tungstate and 0.5 ml of 0.33N H_2SO_4 into a test tube. The test sample was also prepared by pipetting 0.5 ml of 5% dextrose water, 0.5 ml of serum creatinine solution, 0.5 ml of 10% sodium tungstate and 0.5 ml of 0.33N H_2SO_4 into a test tube. All the three samples were properly mixed and centrifuged for 10 minutes.

The 2nd stage involves adding 1 ml each of the supernatant above into their respective test tubes (blank, standard and test samples). One milliliter (1 ml) of picric acid was added into each test tubes followed by 1 ml each of 0.75 M NaOH. All the three test tubes were properly mixed and allowed to stand for 10 mins at room temperature. The absorbance was read at 500 nm wavelength using spectrophotometer (Beckman Coulter DU^{R} 520). The concentration of creatinine was calculated as the absorbance of test sample divided by the absorbance of the standard sample multiply by the concentration of the standard sample. The UMTH reference value for creatinine is 44.0 – 132.0 µmol/L.

Statistical analyses: the data was analyzed using statistical analysis software (SAS) system version 16. Analysis of variance and Student t-test were used to determine significance of association between non-categorical variables. P values less than 0.05 were considered significant, less than 0.01 highly significant and less than 0.001 very significant.

Results

Sumatriptan 50 mg significantly increased the activities of hepatic and renal biochemical analyates and enzymes among patients (Tables 1-4). There was a statistically significant difference in the levels of total bilirubin, conjugated bilirubin, alkaline phosphatase and potassium among the migraineurs ($p<0.001$). Total protein, AST, Cl^- and urea showed highly significant difference among the migraineurs ($p<0.01$). The use of sumatriptan 50 mg also showed a statistically significant difference in the levels of ALT, HCO_3^- and creatinine among the patients studied ($p<0.05$). However, the use of sumatriptan 50 mg did not show any significant difference in the levels of albumin and sodium in this study (Table 1).

Table 1: Effect of sumatriptan 50 mg on hepatic and renal function (N = 30)

LFT & RFT	*Reference value*	*Mean*		*SEM*	*P-value*
		Before therapy	*After therapy*		
Total bilirubin	1.7 - 17.1 µmol/L	6.1	12.7	0.9	0.000***
Conjugated bilirubin	1.7 - 8.5 µmol/L	4.3	6.2	0.3	0.000***
Total Protein	58 – 80 g/L	60.6	65.2	1.6	0.008**
Albumin	35-50 g/L	38.9	40.7	1.2	0.162
Alkaline phosphatase	9 - 35 IU/L	25.3	34.4	2.0	0.000***
AST	≤ 12 IU/L	9.9	14.3	1.6	0.008**
ALT	≤ 12 IU/L	9.2	13.3	1.6	0.013*
Bicarbonate	20-30 mmol/L	22.7	24.5	0.7	0.024*
Chloride	95-110 mmol/L	98.9	101.8	1.0	0.007**
Potassium	2.5-5.0 mmol/L	3.2	3.9	0.2	0.000***
Sodium	135-145 mmol/L	137.1	138.6	1.5	0.316
Urea	2.5-5.8 mmol/L	3.3	3.8	0.2	0.007**
Creatinine	44-132 µmol/L	71.4	91.9	7.5	0.011*

*LFT = Liver function test, RFT = Renal function test, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, SEM = Standard Error Mean (of difference between 'Before' and 'After' therapy), * = Significant p-value (paired Student't' test)*

Sumatriptan 100 mg significantly increased the activities of hepatic and renal biochemical molecules and enzymes among patients except the levels of total protein and sodium. There was a statistically significant difference in the levels of conjugated bilirubin, alkaline phosphatase, AST, HCO_3^- and urea among the migraine patients ($p<0.001$). Total bilirubin, ALT and potassium showed a

highly significant difference among the migraineurs ($p<0.01$). The use of sumatriptan 100 mg also showed a statistical significant difference in the levels of albumin, chloride and creatinine among the migraineurs studied ($p<0.05$) (Table 2).

Table 2: Effect of sumatriptan 100 mg on hepatic and renal function (N = 23)

LFT & RFT	*Reference value*	*Mean*		*SEM*	*P-value*
		Before therapy	*After therapy*		
Total bilirubin	1.7 - 17.1 µmol/L	7.7	12.2	1.5	0.005**
Conjugated bilirubin	1.7 - 8.5 µmol/L	4.4	6.6	0.4	0.000***
Total Protein	58 – 80 g/L	62.1	66.0	2.0	0.057
Albumin	35-50 g/L	38.1	41.0	1.1	0.011*
Alkaline phosphatase	9 - 35 IU/L	18.7	32.7	2.2	0.000***
AST	≤ 12 IU/L	8.9	14.0	1.2	0.000***
ALT	≤ 12 IU/L	8.4	14.8	1.6	0.001**
Bicarbonate	20-30 mmol/L	21.9	24.5	0.6	0.000***
Chloride	95-110 mmol/L	100.7	104.6	1.6	0.022*
Potassium	2.5-5.0 mmol/L	3.3	4.1	0.2	0.001**
Sodium	135-145 mmol/L	138.3	139.3	1.3	0.434
Urea	2.5-5.8 mmol/L	3.2	4.1	0.2	0.000***
Creatinine	44-132 µmol/L	80.5	107.1	9.4	0.010*

*LFT = Liver function test, RFT = Renal function test, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, SEM = Standard Error Mean (of difference between 'Before' and 'After' therapy), * = Significant p- value (paired Student't' test)*

Cafergot® 1 mg showed a statistically significant difference in the levels of conjugated bilirubin among the migraine patients studied ($p<0.001$). Total bilirubin, total protein, albumin, alkaline phosphatase, ALT and urea showed highly significant difference among the migraineurs ($p<0.01$). The use of Cafergot® 1 mg also showed a statistical significant difference in the levels of AST and chloride among the patients ($p<0.05$). However, the levels of HCO_3^-, potassium sodium and creatinine showed no statistical significant difference among the study patients (Table 3).

Table 3: Effect of Cafergot® 1 mg on hepatic and renal function (N = 9)

LFT & RFT	*Reference value*	*Mean*		*SEM*	*P-value*
		Before therapy	*After therapy*		
Total bilirubin	1.7 - 17.1 µmol/L	5.8	13.0	1.5	0.001**
Conjugated bilirubin	1.7 - 8.5 µmol/L	3.7	6.1	0.3	0.000***
Total Protein	58 – 80 g/L	58.0	70.0	3.3	0.008**
Albumin	35-50 g/L	37.7	45.6	2.2	0.007**
Alkaline phosphatase	9 - 35 IU/L	19.4	37.0	3.7	0.001**
AST	≤ 12 IU/L	9.8	18.4	2.7	0.012*
ALT	≤ 12 IU/L	8.7	20.3	3.4	0.009**
Bicarbonate	20-30 mmol/L	23.9	26.8	1.9	0.159
Chloride	95-110 mmol/L	98.6	104.9	2.2	0.019*
Potassium	2.5-5.0 mmol/L	3.3	4.0	0.3	0.051
Sodium	135-145 mmol/L	138.7	141.6	1.7	0.119
Urea	2.5-5.8 mmol/L	3.1	4.5	0.4	0.009**
Creatinine	44-132 µmol/L	93.9	103.2	16.9	0.596

*LFT = Liver function test, RFT = Renal function test, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, SEM = Standard Error Mean (of difference between 'Before' and 'After' therapy), * = Significant p-value (paired Student't' test)*

Cafergot® 2 mg also significantly increased the activities of hepatic and renal biochemical molecules and enzymes among migraineurs with acute attack. There was a statistically significant difference in the levels of chloride among the migraine patients ($p<0.001$). The increase in the levels of total bilirubin, conjugated bilirubin, AST, ALT and HCO_3^- showed highly significant difference among the migraineurs studied ($p<0.01$). The use of Cafergot® 2 mg also showed a significant difference in the levels of total protein, potassium and urea among the patients ($p<0.05$) (Table 4).

Table: 4 Effect of Cafergot® 2 mg on hepatic and renal function (N = 11)

LFT & RFT	*Reference value*	*Mean*		*SEM*	*P-value*
		Before therapy	*After therapy*		
Total bilirubin	1.7 - 17.1 µmol/L	7.8	15.6	1.6	0.001 **
Conjugated bilirubin	1.7 - 8.5 µmol/L	4.1	7.1	0.9	0.008 **
Total Protein	58 – 80 g/L	61.0	70.0	3.0	0.013 *
Albumin	35-50 g/L	38.3	41.1	2.7	0.312
Alkaline phosphatase	9 - 35 IU/L	27.0	35.4	4.2	0.075
AST	≤ 12 IU/L	9.3	20.9	2.6	0.001 **
ALT	≤ 12 IU/L	9.8	21.0	2.4	0.001 **
Bicarbonate	20-30 mmol/L	22.9	26.2	0.9	0.004 **
Chloride	95-110 mmol/L	98.9	105.6	1.0	0.000 ***
Potassium	2.5-5.0 mmol/L	3.2	3.7	0.2	0.047 *
Sodium	135-145 mmol/L	137.8	141.1	1.7	0.082
Urea	2.5-5.8 mmol/L	3.5	4.8	0.6	0.042 *
Creatinine	44-132 µmol/L	79.2	113.5	16.8	0.068

*FT = Liver function test, RFT = Renal function test, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, SEM = Standard Error Mean (of difference between 'Before' and 'After' therapy), * = Significant p-value (paired Student't' test)*

Discussion

Investigation of the effects of sumatriptan (50 mg and 100 mg) on hepatic and renal functions revealed a significant increase in the levels of most biochemical analytes and enzymes among the migraineurs studied. Prior to acute therapy (before drug administration) there was a slight elevation with no statistical significant difference in the levels of alkaline phosphatase (13%), AST (10%) and ALT (7%) above reference hospital value among patients that took 50 mg of sumatriptan tablet. Two weeks after ingestion of 50 mg sumatriptan tablet, there was a significant increase in the levels of ALT, bicarbonate and creatinine ($p<0.05$); total protein, AST, chloride and urea ($p<0.01$); total bilirubin, conjugated bilirubin, alkaline phosphatase and potassium ($p<0.001$).

However, no significant increase in the levels of albumin and sodium ($p>0.05$) was noticed in migraineurs that took 50 mg of sumatriptan tablets. This significant increase in biochemical analytes and enzymes among migraineurs before acute therapy may be attributable to hepatic and renal impairment by the acute migraine attack as previously reported by other related studies [13, 14, 15]. The report of this findings agrees with the report of Sander-Bush and Mayer [8] and Goadsby *et al* [4] in which sumatriptan was reported to be metabolized predominantly by monoamine oxidase-A (MAO-A) and its metabolites exclusively excreted by the kidneys.

Acute migraine attack (before therapy) did not significantly increase the levels of total bilirubin, conjugated bilirubin, total protein, albumin, alkaline phosphatase, AST, bicarbonate, chloride, sodium, potassium and urea above reference hospital value among those that took 100 mg sumatriptan tablets studied. However, 8.6% of patients that took 100 mg of sumatriptan tablet had their ALT and creatinine levels elevated above reference hospital value prior to acute therapy.

The results of this study practically demonstrated that acute migraine headache have a greater potentials of raising the ALT and creatinine levels in susceptible patients. Therefore, monitoring of post administration effects of drugs like sumatriptan on liver and renal function test in this subset of patients needs to be handled with caution to avoid a false positive result. However, acute therapy with sumatriptan 100 mg caused a significant increase in the levels of albumin, chloride and creatinine ($p<0.05$); total bilirubin, ALT and potassium ($p<0.01$); conjugated bilirubin, alkaline phosphatase, AST, bicarbonate and urea ($p<0.001$) when their pretreatment baseline is compared with two weeks post therapy.

This significant increase in biochemical analytes and enzymes among migraineurs may be attributable to hepatic and renal impairment by the drug as previously reported [13, 14, 15]. This also agrees with the report of Goadsby *et al* [4], Sander-Bush and Mayer [8] (2001) and Joan *et al* [26] in which sumatriptan was reported to affect renal and hepatic functions. However, this did not agree with the finding of Razali *et al* [15], Ceriotti [16] and Gras *et al* [27] in which a favourable safety profile with respect to renal, respiratory and hepatic systems was reported.

The effects of Cafergot® (1 mg and 2 mg) on hepatic and renal functions revealed a significant increase in the levels of most biochemical analytes and enzymes among the migraineurs studied two weeks after acute therapy. This findings agrees with the earlier report of Sanders *et al* [18] in which the metabolites of Cafergot could elevates hepatic and renal function test in healthy susceptible individuals. Acute therapy with Cafergot® 1 mg caused a significant increase in the levels of AST and chloride ($p<0.05$); total bilirubin, total protein, albumin, alkaline phosphatase, ALT and urea ($p<0.01$); conjugated bilirubin ($p<0.001$) when the pretherapy is compared with 2 weeks post therapy. However, there is no significant difference in the levels of bicarbonate, potassium, sodium and creatinine ($p>0.05$) when pretherapy is compared with 2 weeks post therapy. Acute therapy with Cafergot® 2 mg

caused a significant increase in the levels of total protein, potassium and urea ($p<0.05$); total bilirubin, conjugated bilirubin, AST, ALT and bicarbonate ($p<0.01$); chloride ($p<0.001$). The levels of albumin, alkaline phosphatase, sodium and creatinine did not differ significantly ($p>0.05$) after acute therapy.

Table 5: Standard activity of AST and ALT in the serum

Absorbance	*U/L*	*Absorbance*	*U/L*
AST			
0.020	7	0.100	36
0.030	10	0.110	41
0.040	13	0.120	47
0.050	16	0.130	52
0.060	19	0.140	59
0.070	23	0.150	67
0.080	27	0.160	76
0.090	31	0.170	89
ALT			
0.025	4	0.275	48
0.050	8	0.300	52
0.075	12	0.325	57
0.100	17	0.350	62
0.125	21	0.375	67
0.150	25	0.400	72
0.175	29	0.425	77
0.200	34	0.450	83
0.225	39	0.475	88
0.250	43	0.500	94

AST = Aspartate aminotransferase, ALT = Alanine aminotransferase

The impact of Cafergot® on the liver and renal function observed in this study could be attributable to the generation of active metabolites (potential free radicals) in the liver by largely undefined pathways and significant percent of such metabolites normally do get excreted through the bile and kidneys. The elevation in the hepatic enzymes and renal analytes due to Cafergot® observed in this study did not appear to be dose dependent. This finding agrees with the report of Perrin [28] where generated free radicals from Cafergot® induce liver damage in susceptible individuals. Results of this study support the findings of Karia *et al* [29] and Sanders *et al* [18] that chronic ergotamine therapy causes a tubulo-interstitial nephritis and renal infarction. The specific mechanism of interstitial nephritis is not clear; it is highly probable that prolonged ischaemia of the renal interstitium could be responsible.

Conclusion

Acute migraine attack did not significantly elevates the levels of most hepatic and renal biochemical analytes and enzyme among migraineurs studied, but sumatriptan and Cafergot® therapy showed a significant increase in most of the biochemical analytes and enzyme (except sodium) among the migraine patients studied.

Therefore, concomitant administration of these drugs with others needs to be properly evaluated in other to prevent potential drug interaction. Furthermore, in order to elucidate the actual role of sumatriptan and Cafergot® with respect to LFT and RFT in acute migraine therapy, prospective controlled studies are needed.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests