Iraqi JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-alnahrain.edu.iq
http://www.iraqijms.net

Effects of Cytochrome p-450 Inducer and Inhibitor Antiepileptic Drugs on Lipid Profile in Normal and Diabetic Rabbits

Mohammed A.M. Abdul-Bari[1] *MSc*, **Faruk H. Al-Jawad**[2] *PhD,* **Haitham M. Kadhim**[3] *PhD*

[1,3]Dept. of Pharmacology, Collage of Medicine, Al-Nahrain University, [2]Al-Yarmouk University College, Baghdad, Iraq.

Abstract

Background Anticonvulsants drugs are a diverse group of pharmacological agents used in the treatment of epileptic seizures are known to inhibit or activate cytochrome p-450 enzymes that play a crucial rule in the metabolic process.

Objective To investigate any possible differences in the effect of antiepileptic drugs; enzyme inducer (carbamazepine) and enzyme inhibitor (lamotrigine) on lipid profile in normal and diabetic rabbits depending on its effect on cytochrome p-450 enzymes.

Methods Fifty four healthy domestic rabbits of both sexes weighing 0.5-2.5 kg were studied. They were divided into group A (standard) received tolamatrigine and carbamazepine without induction of diabetes and group B (received the same regimen) with induction of diabetes. Lipid profile was tested in the two groups.

Results Carbamazepine-treated group showed a significant increase in the lipid profile at day 20 of treatment compared to day 5 in comparison with induced and non-induced control groups and control group in normal and diabetic rabbits. Lamotrigine showed less effect on lipid profile; and in non-diabetic treated groups it showed a non-significant change in lipids level as compared to the control group.

Conclusions Anti-epileptics drugs that possess an enzyme inducing effect as carbamezpin tend to induce high lipids profile in comparison to lamotigine.

Keyword Lamotrigine, carbamazepine, anticonvulsants, glucose, lipid.

List of abbreviation: CYP450 = cytochrome P450, AEDs = new antiepileptic drugs, CBZ = carbamazepine, FBG = fasting blood glucose, TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, VLDL-C = very low-density lipoprotein cholesterol

Introduction

Cytochrome P450 (CYP450) is a group of enzymes present in every type of cell in the body except red blood cells and skeletal muscle cells. They are important in metabolizing substances normally present in the body such as steroids, fat-soluble vitamins, fatty acids, prostaglandins, and alkaloids. The P450 enzymes also detoxify drugs and a great number of environmental pollutants, such as carcinogens present in tobacco smoke and charcoal-broiled meat, polychlorinated biphenyls, and dioxin. CYP450, which is the main enzyme involved in the drug metabolism, was published in 1958. Since then, it has become clear that CYP450 is a superfamily of enzymes with more than 200 family members. The CYP450 enzyme system is responsible for the metabolism of a wide range of endogenous and exogenous substrates [(1,2)].

By catalyzing the first steps in different pathways of cholesterol degradation, CYP450 play key roles in cholesterol homeostasis [(3)].

Although many new antiepileptic drugs (AEDs) have been introduced over the past 15 years, the consensus first choice for focal seizures has

traditionally been carbamazepine (CBZ) which exhibits a potent induction of the CYP450 enzyme system [4].

CYP450 enzymes are known to figure prominently in numerous important aspects of metabolism as in lipid metabolism on the other hand also an inhibition of CYP450 enzymes has shown to affect the metabolic process and so affect the levels of lipid profile [5].

The aim of the study is to investigate any possible differences in the effect of AEDs on lipid profile depending on its effect on CYP450 enzymes.

Methods

Fifty four healthy domestic rabbits of both sexes weighing 0.5-2.5 kg were used in the present study. They were supplied from Center of Technical Institution, Al-Nahrin University. They housed one per cage, which is provided with a wire mesh floor. They were kept in a well-controlled hygienic environment and water was given *ad libitum*.

Animal design

Animals were allocated into group A (standard) received lamotrigine (lamictal®) 25 mg/kg (GsK, Poland) and CBZ (Tegertol ®) 90 mg/kg (Novartis, Switzerland) and group B (received the same regimen) plus they were subjected into induction of diabetes.

Induction of Diabetes

The rabbits were injected with alloxan monohydrate dissolved in sterile saline (0.9% NaCl) at a single dose of 150 mg/kg intraperitoneally. The baseline fasting blood glucose (FBG) was determined before intraperitoneal administration of alloxan. After 6 hr of alloxan administration, 5% glucose solution was infused orally in the feeding bottle for a day to overcome the early hypoglycemic phase as a result of acute massive pancreatic release of insulin. Hyperglycemia was confirmed by elevated serum glucose level, determined at 3rd day post-induction. The rabbits that became hyperglycemic (FBG level around 200-250 mg/dl) and stable were include in the study [6].

Measurement of serum lipid profile

The level of lipid profile was measured at day 5 and day 20 post-treatment.

Serum total cholesterol determination

Serum total cholesterol (TC) was estimated according to the method of Allain (1974) where a readymade kit is used for this purpose, based on the oxidation of cholesterol, which resulted in the formation of H_2O_2, and when the latter is reacted with phenol, a red colored quinonimine was formed and the intensity of color was measured at 505 nm and compared with standard cholesterol solution [7].

Serum triglyceride determination:

Serum triglyceride (TG) levels were determined according to the method of Fossati and Prencipe (1982) and a readymade kit was utilized for this purpose, based on enzymatic oxidation of the glycerol-3-phosphate, which is generated from the hydrolysis of TG moiety. The oxidation process resulted in the formation of H_2O_2, which is measured spectrophotometrically as indicated before [8].

Determination of serum high and low density lipoprotein cholesterol

Serum high-density lipoprotein cholesterol (HDL-C) levels were estimated according to the method of Burstein et al (1970) through which low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) was determined calorimetrically by measurement of light absorbance at 505 nm, using a readymade kit for this purpose [9].

Result

The TC level of the control group was 67.66 ± 4.5 mg/dl at day 5 and 68.6 ± 4.5 mg/dl at day 20 of the study. The CBZ-treated group showed significant difference ($p < 0.05$) when compared to control group with 3.8 % increment in the total mean value of

cholesterol. On the other hand, lamotrigine-treated group demonstrated a non-significant difference when compared to the control group plus 0.8 % increment in the total mean value of cholesterol.

The TC in CBZ-treated group was 68.3 ± 2.5 mg/dl at day 5 and increased to 73 ± 2.6 mg/dl at day 20 ($p < 0.05$). The percentage of change equals to 6.8 %. Moreover, the TC in the lamotrigine-treated group was 69.0 ± 3.0 mg/dl at day 5 and 68±5 mg/dl at day 20. The percentage of change was 1.4% with no significant differences between day 5 and day 20 of the study (Table 1).

Table 1. Cholesterol level at day 5 and day 20 of the study for the control group and treated groups

Days of treatment	Blood cholesterol level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	67.66 ± 4.50	68.33 ± 2.51	69.00 ± 3.00
20	68.66 ± 4.0	73.0 ± 2.64	68.0 ± 5.00
Total	67.91 ± 3.50	70.50 ± 2.90	68.50 ± 3.7
*	---	$p < 0.05$	ns
**	---	$p < 0.05$	ns
†	---	3.8%	0.8%
‡	1.47%	6.8%	1.4%

* = treated Vs control group, ** results on day 5 vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

The TC level was 183 ± 3.6 mg/dl at day 5 and 200±5 mg/dl at day 20 of the study. The CBZ-treated group showed significant difference ($p < 0.01$) as compare to the control group with 6.6 % increment between the mean values whereas, lamotrigine-treated group show a non-significant change compared to the control group.

In the CBZ-treated group, TC level was 183±3 mg/dl at day 5 and increased to 220.66±4.04 mg/dl at day 20 ($p < 0.001$) with 20.2 % increment. Considering lamotrigine-treated group, TC level was 186 ± 2.0 mg/dl at day 5 and increased to 190.3 ± 2.3 mg/dl at day 20 ($p < 0.01$) with 2.3% increment (Table 2).

Table 2. Cholesterol level at day 5 and day 20 of the study for the standard control and treated diabetic groups

Days of treatment	Blood cholesterol level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	183.00 ± 3.6	183.0 ± 3.00	186.0 ± 2.00
20	200.00 ± 5.0	220.6 ± 4.04	190.3 ± 2.3
Total	188.33 ± 7.91	200.91 ± 16.04	188.03 ± 3.42
*	---	$p < 0.01$	ns
**	---	$p < 0.001$	$p < 0.01$
†	---	6.6%	-0.1%
‡	9.2%	20.2%	2.3%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

The TG level of the standard control group was 85 ± 5 mg/dl at day 5 and 86 ± 3 mg/dl at day 20 of the study. CBZ-treated group showed significant difference ($p < 0.001$) as compared to the control group with 51.6 % increment between the total mean values. Meanwhile, Lamotrigine-treated group showed non-significant changes in comparison to the control group with only 0.16% increment. CBZ-treated group demonstrated significant increment ($p < 0.001$) from day 5 (86.0 ± 1.0 mg/dl) to 160±5 mg/dl on day 20, with 86% increment within the same group. Moreover, lamotrigine-treated group show no change in the blood TG level between day 5 and day 20 (86.0 ± 3.0 mg/dl versus 85.3 ± 3.04 mg/dl) with only 0.8 % increment (Table 3).

Table 3. Triglyceride level at day 5 and day 20 of the study for the standard control and treated groups

Days of treatment	Blood triglyceride level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Carbamazepine
5	85.0 ± 5	86.00 ± 1	86.00 ± 3
20	86.00 ± 3	160.00 ± 5	85.30 ± 3.04
Total	85.25 ± 2.9	129.25 ± 31.7	85.34 ± 2.31
*		p < 0.001	ns
**		p < 0.001	ns
†		51.6%	0.16%
‡	1.17%	86%	-0.8%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

The TG level of the positive control group was 133.6 ± 4.04 mg/dl at day 5 and 153.6 ± 3.2 mg/dl at day 20 of the study. CBZ-treated group showed significant difference ($p < 0.01$) as compared to the control group with 23% increment between the total mean values. Meanwhile, Lamotrigine-treated group showed non-significant changes in comparison to the control group with only 0.15% decrement. CBZ-treated group demonstrated significant increment ($p < 0.01$) from day 5 (130.3 ± 2.5 mg/dl) to 246 ± 5.2 mg/dl on day 20, with 88.7% increment within the same group. Moreover, lamotrigine-treated group showed increased blood TG level significantly ($p < 0.01$) between day 5 and day 20 (135.3 ± 2.5 mg/dl versus 161 ± 4.5 mg/dl) with only 18.9 % increment (Table 4).

The LDL level of the standard control group was 46 ± 3 mg/dl at day 5 and 45 ± 1 mg/dl at day 20 of the study. Lamotrigine-treated group showed non-significant changes in comparison to the control group with only 0.4% increment; whereas, CBZ-treated group showed significant difference ($p < 0.05$) as compared to the control group with 33.7 % increment between the total mean values. Meanwhile, CBZ-treated group demonstrated significant increment ($p < 0.001$) from day 5 (45.0 ± 2.0 mg/dl) to 60.2 ± 0.72 mg/dl on day 20, with 33.7% increment within the same group. Moreover, lamotrigine-treated group show no change in the blood LDL level between day 5 and day 20 (44.33 ± 4.5 mg/dl versus 45.8 ± 0.2 mg/dl) with -0.6% decrement (Table 5).

The HDL level of the standard group was 32.6 ± 1.5 mg/dl at day 5 and 33.6 ± 0.5 mg/dl at day 20 of the study. Lamotrigine-treated group showed non-significant change in comparison to the control group with -2.4 % decrement; whereas, CBZ-treated group showed a significant difference ($p < 0.05$) as compared to

control group with 6.2% increment between the total mean values. Furthermore, CBZ-treated group demonstrated non-significant difference in HDL level at day 5 (32.0 ± 2.0 mg/dl) versus 37 ± 4 mg/dl at day 20 with 15% increment. Similarly, lamotrigine-treated group showed non-significant differences (33.0 ± 2.0 mg/dl at day 5 versus 32.0 ± 0.4 mg/dl at day 20) with 2.6 % decrement (Table 6).

Table 4. Triglyceride level at day 5 and day 20 of the study for the standard control and treated diabetic groups

Days of treatment	Blood Triglyceride level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	133.66 ± 4.04	130.33 ± 2.51	135.33 ± 2.51
20	153.66 ± 3.21	246.00 ± 5.29	161.0 ± 4.58
Total	144.33 ± 8.45	177.50 ± 46.10	144.08 ± 10.79
*		p < 0.01	NS
**		p < 0.01	p < 0.01
†		23%	-0.15%
‡	8%	88.7%	18.9%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

Table 5. Low-density lipoprotein level at day 5 and day 20 of the study for the standard control and treated groups

Days of treatment	Blood low-density lipoprotein level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	46.00 ± 3	45.0 ± 2	44.33 ± 4.5
20	45.00 ± 1	60.2 ± 0.72	45.8 ± 0.2
Total	45.5 ± 2.71	50.8 ± 6.45	45.2 ± 2.07
*		p < 0.05	ns
**		p < 0.001	ns
†		11.6%	-0.6%
‡	-2%	33.7%	- 3.38%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

The LDL level was 100.3±4.5 mg/dl at day 5 and 120±5 mg/dl at day 20 of the study. The CBZ- and lamotrigine-treated groups showed non-significant difference as compare to the control group. CBZ-treated group demonstrated significant increment (p < 0.001) in LDL level (98.6 ± 4 mg/dl at day 5 as compared to 144.6 ± 5 mg/dl at day 20) with 46.6 % increment between the mean values Likely, lamotrigine-treated group show significant increment (p < 0.01) in LDL level (102 ± 2.6 mg/dl at day 5 versus 124 ± 1.1 mg/dl at day 20 with 22.4% increment (Table 7).

The HDL level of the control group was 27.3±4.04 mg/dl at day 5 and 20±5 mg/dl at day 20 of the study. The CBZ-treated groups showed significant difference (p < 0.05) as compare to the control group with 20.5%

increment. CBZ-treated group showed HDL level of 28 ± 3 mg/dl at day 5 and increased significantly ($p < 0.05$) as compared to 31 ± 4.5 mg/dl at day 20 with 11.7 percent change. Lamotrigine-treated group demonstrated significant decrement ($p < 0.05$) in HDL level (26.6 ± 3.5 mg/dl at day 5 versus 19.8 ± 0.76 mg/dl at day 20 with 25.4 % percent change (Table 8).

Table 6. High-density lipoprotein level at day 5 and day 20 of the study for the standard control and treated groups

Days of treatment	Blood high-density lipoprotein level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	32.6 ± 1.5	32.00 ± 2.0	33.0 ± 2
20	33.66 ± 0.57	37.00 ± 4.0	32.23 ± 0.4
Total	33.41 ± 0.99	35.50 ± 3.17	32.55 ± 1.67
*		p < 0.05	ns
**		ns	ns
†		6.2%	-2.4%
‡	3%	15%	-2.6%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

Table 7. Low-density lipoprotein level at day 5 and day 20 of the study for the standard control and treated diabetic groups

Days of treatment	Blood low-density lipoprotein level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	100.33 ± 4.5	98.66 ± 4.04	102.00 ± 2.64
20	120.0 ± 5	144.6 ± 5.03	124.93 ± 1.1
Total	111.41 ± 8.7	114.75 ± 19.63	112.31 ± 10.05
*		p < 0.05	ns
**		p < 0.001	p < 0.001
†		2.9%	0.8%
‡	19.6%	46.6%	22.4%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

Discussion

Animal data showed that a particular enzyme of CYP450, CYP51A1, catalyzes the conversion of lanosterol into cholesterol intermediates. When these intermediates build up through inhibition of the enzyme, they in turn inhibit the rate-limiting step of cholesterol synthesis, 3-hydroxy-3- methylglutaryl-coenzyme A reductase (HMG-CoA reductase), and slow the synthesis of cholesterol [(7)]. It follows that induction of CYP51A1 should therefore increase cholesterol production through metabolism of these intermediates and reduced feedback inhibition. The increased activity of the cholesterol synthesis rate limiting (enzyme HMG-CoA reductase) may also lead to increase in LDL-C levels [(3)].

On the other hand CYP450 enzymes play a role in the synthesize of polipoprotein A (the main HDL lipoprotein particle) leading to increased concentration of HDL-C level in the blood [10].
There is a strong evidence that drugs assumed to have an inhibitory or stimulatory effect on CYP450 enzymes had an effects on lipid profile, like ketoconazole which is potent CYP450 inhibitor that has been shown to reduce cholesterol production in studied animal and this effect is documented clinically by the finding that patients taking valproate, (CYP450-inhibiting properties) have lower TC levels than controls [11].

Table 8. High-density lipoprotein level at day 5 and day 20 of the study for the standard control and treated diabetic groups

Days of treatment	Blood high-density lipoprotein level (mg/dl)		
	Control group	Treatment group	
		Carbamazepine	Lamotrigine
5	27.33 ± 4.04	28.00 ± 3	26.6 ± 3.51
20	20.00 ± 5	31.33 ± 4.5	19.83 ± 0.76
Total	24.33 ± 4	29.33 ± 3.33	24.07 ± 3.71
*		p < 0.05	ns
**		p < 0.05	p < 0.05
†		20.5 %	-0.01 %
‡	-26.7%	11.7%	-25.4%

* = treated Vs control group, ** results on day 5 Vs day 20 in the same group. † = percentage of change between each treated group Vs control group, ‡ = percentage of change between day 5 and day 20 of the same group.

These findings suggest that serum lipids parallel to the activity of the CYP-450 enzyme system, so that treatment with a CYP450 inducing agent increases lipids, and upon withdrawal of the drug lipids return to the baseline [12].
In the present study the drugs that had been chosen has different effect on CYP450 from enzyme induction (CBZ) to enzyme inhibitor (lamotrigine) and so it is suspected to differ in their effect on lipid profile. Research found that AEDs which induces the CYP450 will alter the metabolism in a variety of ways that may become apparent when the patients are started on or taken off these drugs [13].
Mintzer et al [14] covered this possible effect in his researcher he found that patients switched from enzyme-inducing agent phenytoin to the non-inducing drugs levetiracetam will experience a sizable drop in serum lipids, along with changes in other serologic indices of vascular risk.
Other researcher Abou-Khalil [15] found that epileptic patients switched from an enzyme inducer (CBZ) to non-inducer drug like lamotrigine shows significant increase and produces rapid and clinically significant amelioration in several serological markers of vascular risk.
Compared to the control group, CBZ-treated patients may have higher lipid levels than controls; at least one such study measured before and after treatment found that CBZ produces significant elevation of lipids in blood [11].
Studying the correlation between CBZ and high lipid profile level and its relation to lipid profile and so on atherosclerosis has been done also by Brämswig et al [16]. The investigators concluded that significant lipid alterations were observed in CBZ-treated patients with epilepsy in comparison with healthy control subjects.
These results compatible with the results obtained in the present study as it was found that CBZ-treated group showed significant

increase in blood TC, TG, LDL, and HDL levels both in cases of day 5 versus day 20 results of the study and when comparing the results with the control group in normal and diabetic rabbits.

On other hand, lamotrigine exhibited less effect on lipid profile, in non-diabetic treated groups it showed a non-significant change in lipids levels in compared to the control group.

In the diabetic-treated group, it showed a significant increase in TC, TG, HDL levels from day 5 to day 20 in comparison to the same group where as in comparison to the positive control group it showed non-significant increase in all lipid profiles levels. These results reflect no significant effect of lamotrigine in both normal and diabetic rabbits while the increase in diabetic group from day 5 to day 20 was similar to the increase in the positive control group this estimate that the increase is due to the effect of diabetes on lipid profile rather than the effect of drug itself.

We conclude that AEDs that possess an enzyme inducing effect as CBZ tend to have high lipids profile in comparison to lamotrigine (AEDs with no enzyme induction effect). This is very important in both normal and diabetic condition as AEDs can be given to non-diabetic patient or to diabetic one for treatment of neurological and psychological diseases. These effects could be vital for patient suffering from other diseases as cerebrovascular accident, angina, heart failure and hyperlipidemia

Acknowledgements

We are grateful to all staff of the Department of Pharmacology in the College of Medicine, Al-Nahrain University.

Author contribution

Dr. Abdul-Bari collected the data and analyzed it; Dr. Al-Jawad arranged it and supervised the study; and Dr. Kadhim interpreted and arranged drafting of this paper.

Conflict of interest

There is no conflict of interest that could be perceived.

Funding

No specific grant from any funding agency.

References

1. Benko B, Kalász H, Ludányi K, et al. In vitro and in vivo metabolisms of K-48. Anal Bioanal Chem. 2007; 389: 1243-7.
2. Ahmed E, Nagaoka K, Fayez M, et al. Long-term p-nitrophenol exposure can disturb liver metabolic cytochrome P450 genes together with aryl hydrocarbon receptor in Japanese quail. Jpn J Vet Res. 2015; 63: 115-27.
3. Gibbons GF. The role of cytochrome P450 in the regulation of cholesterol biosynthesis. Lipids. 2002; 37: 1163-70.
4. Ceron-Litvoc D, Soares BG, Geddes J, et al. Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. Hum Psychopharmacol. 2009; 24: 19-28.
5. Zona C, Avoli M. Lamotrigine reduces voltage-gated sodium currents in rat central neurons in culture. Epilepsia. 1997; 38: 522-5.
6. Viswanathaswamy AHM, Koti BC, Gore A, et al. Antihyperglycemic and antihyperlipidemic activity of plectranthusamboinicus on normal and alloxan-induced diabetic rats. Indian J Pharm Sci. 2011; 73: 139-45.
7. Allain CC, Poon LS, Chan CS, et al. Enzymatic determination of total serum cholesterol. Clin Chem. 1974; 20: 470-5.
8. Fassati P, Principe L. Measurement of serum triglyceride colorimetrically with an enzyme that produce H_2O_2. Clin Chem. 1982; 28: 2077-80.
9. Burstein M, Scholink HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res. 1970; 11: 583-9.
10. Calandre EP, Rodriguez-Lopez C, Blazquez A, et al. Serum lipids, lipoproteins and apolipoproteins A and B in epileptic patients treated with valproic acid, carbamazepine or phenobarbital. Acta Neurol Scand. 1991; 83: 250-3.
11. Nikolaos T, Stylianos G, Chryssoula N, et al. The effect of long-term antiepileptic treatment on serum cholesterol (TC, HDL, LDL) and triglyceride levels in adult epileptic patients on monotherapy. Med Sci Monit. 2004; 10: MT50-2.
12. Mintzer S, Boppana P, Toguri J, et al. Vitamin D levels and bone turnover in epilepsy patients taking

carbamazepine or oxcarbazepine. Epilepsia. 2006; 47: 510-5.

13. Johannessen IS, Landmark JC. Antiepileptic drug interactions - principles and clinical implications. Curr Neuropharmacol. 2010; 8: 254-67.

14. Mintzer S, Skidmore CT, Abidin CJ, et al. Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol. 2009; 65: 448-56.

15. Abou-Khalil BW. The far-reaching influence of hepatic enzyme-inducing antiepileptic drugs. Epilepsy Curr. 2009; 9: 158-9.

16. Brämswig S, Sudhop T, Luers C, et al. Lipoprotein (a) concentration increases during treatment with carbamazepine. Epilepsia. 2003; 44: 457-60.

Correspondence to Mohammed A.M. Abdul-Bari
E-mail: mohammed_abdulmutalib@yahoo.com
Received 20th Sep. 2015: Accepted 28th Feb. 2016