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Population pharmacokinetics of Carbamazepine and optimising its use in Saudi epileptic children

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ABSTRACT

The objective of this study is the identification of Carbamazepine (CBZ) phamacokinetic parameters (PKP) and to suggest CBZ optimal therapeutic range (OTR) to Saudi epileptic children (SEC). 493 SEC with means age 8.23 ± 3.907 years, body weight 26.18 ± 12.10 kg, were all treated with CBZ, therapeutic drug monitoring (TDM) at Drug Monitoring Unit (DMU). In the retrospective (RS), 603 samples of 186 males and 155 females were from medical records at King Abdulaziz University Hospital (KAUH). Patients, diagnoses, clinical and laboratory investigations were taken from Maternity & Children Hospital. In the prospective (PS), 255 samples from 92 males and 48 females were placed on CBZ maintenance dose (MD) of 442.859 ± 184.44 mg/day. In the pharmacokinetics (PK-S), 6 males and 6 females had no CBZ before. Given a single loading dose (LD) with mean 4.19 ± 1.64 mg/kg, 4 to 8 samples were collected for calculation of PKP. For OTR determination, CBZ MD sampling continued up to 4 months. The following results were obtained: (a) Pharmacokinetic Parameters - Cl [(L/h)/kg] = 0.3526 ± 0.233; Ke (h^{-1}) = 0.0837 ± 0.056; Cmax (mg/ml) = 2.52 ± 1.447; $T_{1/2}$ (h) = 11.68 ± 6.88; Tmax (h) = 4.38 ± 1.992; Vd (L/kg) = 6.47 ± 6.022; AUC [(µg/ml)/h] = 13.49 ± 6.0904. (b) Samples distribution (%) for RS and PS: 73.63, 92.5 therapeutic range, 22.22, 6.27 sub therapeutic, 4.15, 1.23 toxic, respectively. (c) One week after treatment, 83.3% were seizure free, a patient continued after the 1st month. Correlation was stronger between seizures numbers VS blood levels µg/ml (r = -0.97) than VS dose mg/kg BW (r = -0.92). (d) Toxicity: 2- Steven Johnson Syndrome, 1- osteoporosis and 1- dynamic/kinetic interaction. In conclusion, actual CBZ PKP values in SEC were defined. No direct correlation between ethnicity and blood levels. Similarity to findings conducted on non-Saudi healthy or adult volunteer confirms the importance of continuing this work using modern technology to differentiate between the genuine CBZ PKP values and influences by interfering modifiers.

Keywords: Epilepsy, pharmacokinetic, Carbamazepine.

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INTRODUCTION

Epilepsy is a psychological, social and neurological debilitating condition affecting 50 millions worldwide. Many people develop epilepsy as children or teenagers. Others develop it later in life (Hauser, 1992; Hauser, 1994).

Recurrent seizures for no obvious reason are the most common symptom of epilepsy. Most seizures last only a few seconds or minutes and vary from person to person. Epileptic seizures fall into two main categories: partial and generalized (Children's Medical Centre, University of Virginia, 1996).

The incidence of this disease in developed countries ranges from 24 to 53/100,000. Although there is no confirmatory study yet published, the incidence in Saudi Arabia seems to be higher, most likely due to increase of risk factors for symptomatic seizure disorder and inherited epilepsy, individuals with epilepsy have a mortality rate of 2103 times that of the general population. This rate is even higher in developing countries (KFSH, 2004).

Carbamazeoine (CBZ) became one of the cornerstones of anticonvulsant therapy in the paediatric population, where it is used in partial complex, generalized tonic-clonic, mixed seizure disorders and other partial or

generalized seizures (Seetharam and Pellock, 1991; McKichan, 1986). Carbamazepine has been used as AEDs since 1965, and is most effective against partial seizures (Ghamari et al., 2013).

Serum concentrations of CBZ appear to correlate well with therapeutic response. In accordance to empirical data, most patients' concentration between 4 to 12 µg/ml result in seizure control without significant dose-related adverse effects (Children's Medical Centre, University of Virginia, 1996). However like other AED, clinicians should be aware of the highly patient specific response to CBZ. A peak plasma level is achieved in 6 to 24 h after a single oral dose.

CBZ has a large volume of distribution (Vd), estimated to be 1 to 2 L/kg, and is approximately 75 to 85% protein bound and approximately 2 to 3% excreted unchanged in the urine. Protein binding may be decreased in infants, resulting in a greater proportion of free (active) drug (MacKichan, 1986; Ghamari et al., 2013).

CBZ undergoes extensive hepatic metabolism through the cytochrome P450 enzyme system. It induces its own metabolism, which cause increased clearance (Cl) and decreased serum levels when dosing is initiated or modified. In adults, the elimination half life following a single dose ranges from 11 to 30 h. Half-life declines to approximately 5 to 14 h with chronic doses. Similar values have been reported to children (Seetharam and Pellock, 1991).

METHODOLOGY

12 patients (6 females and 6 males), age 1 to 14 years (mean 7.58 ± 3.777) and body weight 9.10 to 42.40 kg (mean 24.06 ± 10.75) attending the MCH- Jeddah who met the selection criteria diagnosed to have partial or generalized epilepsy, had no other chronic illness, no impaired liver or renal function and had not received CBZ before or had no CBZ since at least one month before entering into the study. Prior to the administration of CBZ, mothers of patients were given instruction guidelines regarding the food intake and other precautions.

Each patient was given a loading dose (LD) of CBZ suspension (Eptol- Tabuk Pharmaceutical Co, Tabuk, KSA) amounting to 2 folds of the prescribed initial dose (mean 4.19 ± 1.64 mg/kg) (Table 1).

Blood samples for CBZ concentrations and determination of CBZ pharmacokinetic (PK) parameters were collected from each patient pre and post CBZ LD treatment at 0, 2, 4, 6 and 8 h, after the LD; then during subsequent CBZ maintenance dose (MD) treatment on the 5th, 15th and 30th days and on the 2nd, 3rd and 4th month follow-up period at their visits to their treating doctors at the hospital.

Patients were grouped according to age to determine the variability of response to CBZ treatment of children into different age groups:

Group 1: Patients from 1 to 5 years old
Group 2: Patients from 6 to 9 years old
Group 3: Patients from 10 to 14 years old

CBZ dose for the 12 patients was adjusted in accordance to PK principles as well as to the individual patients' needs by the prescribing physicians.

CBZ PK parameters were calculated (Table 4a to c) using the conventional PK equations (Dhillon and Gill). Individual peak plasma drug concentration (Cmax) and time taken to reach peak plasma concentration (Tmax) were determined by inspection of the observed plasma drug concentration –time data consequent to the relatively low number of points contained on the absorption phase and their inherent variability. The area under the plasma concentration time curves from 0 to 8 h post loading dose (AUC_{0-8}) per patient was determined using the log-linear trapezoidal rule. The elimination rate constant (Ke) was determined by first graphically plotting the log plasma concentration vs. time of the concentration and then using the conventional formula in determining Ke. Clearance (Cl/F), (where F is the relative bioavailability values = 87%) (Arafat, 2003) for each patient were determined as dose per AUC_{0-8}. The elimination half life ($t_{1/2}$) was calculated as 0.693/ Ke. The volume of distribution (Vd/F) was determined by the conventional equation Cl / Ke.

Statistical analyses were performed using SPSS-Statistical Package version 11.0 for Windows (SPSS Inc., Microsoft Corp. Chicago, IL, USA). CBZ PK parameters for the study cohort were examined by using standard descriptive statistics (mean, standard deviation and range).

Hematological, biochemical, enzymological and electrolytes were carried out together with hospital routine laboratory investigations and the obtained values from patients have been compared with the reference control of normal values used by the hospital.

RESULTS

CBZ plasma concentrations of the 12 patients at a time interval of 0, 2, 4, 6 and 8 h after the loading dose showed that only patient no. 10 had achieved therapeutic blood level (TBL) (Figure 1).

However, on 5th, 15th and 30th day of treatment, 75% (9/12), 75% (9/12) and 78% (7/9) obtained TBL, respectively. Patient no. 4 dropped into the sub-therapeutic range (STR) on the 5th day but obtained TBL on the 15th day. Patient no. 5 remained sub-therapeutic until the 30th day but obtained TBL on the 60th day. Patient no. 9 was in the TBL in the 5th day but became sub therapeutic on the 15th day but obtained TBL again on the 30th day (Figure 2).

The different blood levels during the first month showed that out of the 33 blood samples, there were: 26 TBL, 5 STL and 2 Toxic (TxL) samples (Figure 2). While during the second and third month, out 15 blood samples, 10 were TBL and 5 were TxL (Figure 2).

Three months follow-up of the 5 patients which have available data showed that 80% obtained TBL on the 60th, 100% on the 90th and 40% on the 120th day. Patient no. 7 was in the toxic range in the 60th day from treatment but became therapeutic on the 90th day and went toxic again on the 120th day (Figure 2).

Hgb, MCV, MCH and platelets are in the normal range in 6 patients, while the other 6 patients developed anemia; 4 were anemic from the beginning and became severe anemic while 2 were within the normal range at the start but became anemic during CBZ treatment.

The hepatic liver enzymes SGOT, SGPT and GGT tests show that 83.3% of the patients were in the normal range while 16.7% showed highly increasing levels of

Table 1. Demographic data of the 12 patients and their dose/body weight and dose/body surface area.

Patients	Age	sex	Loading dose (mg)	Dose/wt (mg/kg)	Dose/BSA (mg/m^2)
1	6	F	60	2.89	73.79
2	14	M	80	3.06	77.36
3	12	M	150	2.99	86.37
4	1	F	40	4.40	96.48
5	9	M	120	2.83	95.52
6	12	M	100	2.43	76.70
7	10	F	120	5.63	137.62
8	4	M	100	6.67	158.53
9	5	F	100	6.17	147.60
10	9	F	200	6.67	195.18
11	7	M	60	3.16	76.03
12	4	F	48	3.56	79.18
Mean STDEV	7.58 ± 3.777			4.1934 ± 1.635	108.363 ± 40.782

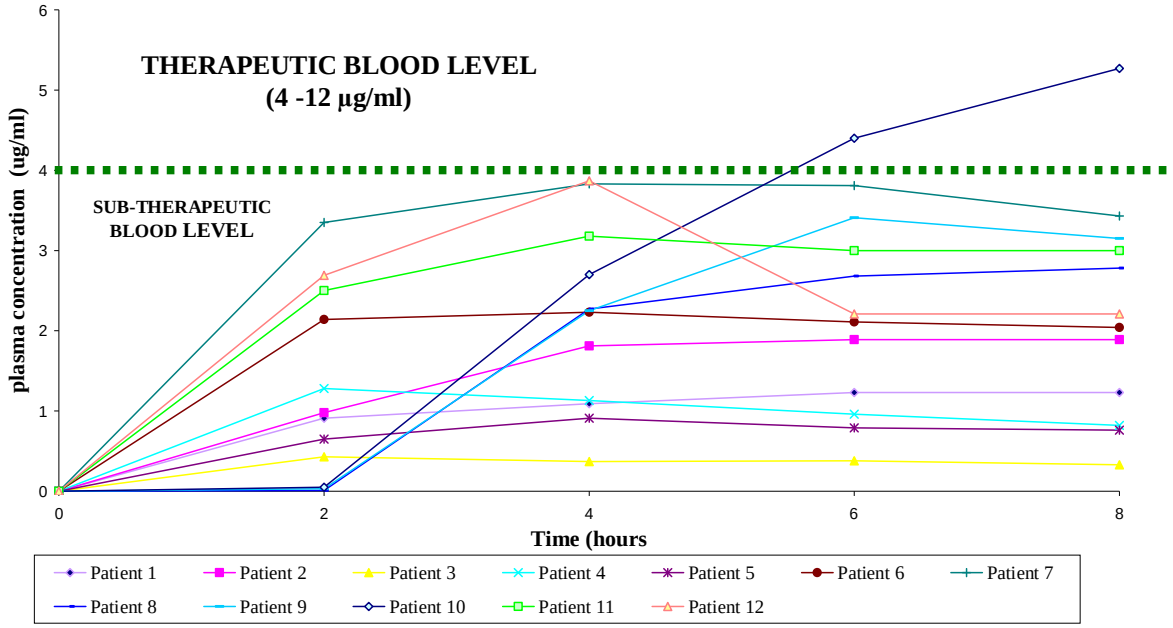

Figure 1. CBZ plasma concentration-time profile for 12 patients after the loading dose.

these enzymes. The total bilirubin (T-bil) was found in the normal range in all patients, while only 58% were in the normal range for Alkaline Phosphatase (AP).

The kidney related enzyme BUN was elevated in 92% of patients (29.64 ± 11.18). Creatinine (Cr) level increased with increase in CBZ doses but within the normal range. Sodium (Na) and Potassium (K) were in the normal range.

Before CBZ treatment, all 12 patients experience seizures in various frequencies. Following the duration of CBZ treatment during the first month, 92% were free of seizure while patient no. 5 continued having attack although his CBZ dose was increased to 300 then to 420 mg/day on the 5th and 15th day of treatment respectively (Table 2).

In order to establish the relation between PK and pharmacodynamic (PD) CBZ effect, the 12 patients were sub-divided into the following groups:

Group A: Frequency of seizure attacks ranged from 1 to 3 times daily
Group B: Frequency of seizure attacks ranged from 1 to 3 times per week
Group C: Frequency of seizure attacks ranged from 1 to 2 times per month

There are strong correlation between the CBZ dose/body weight, CBZ plasma concentration and the number of

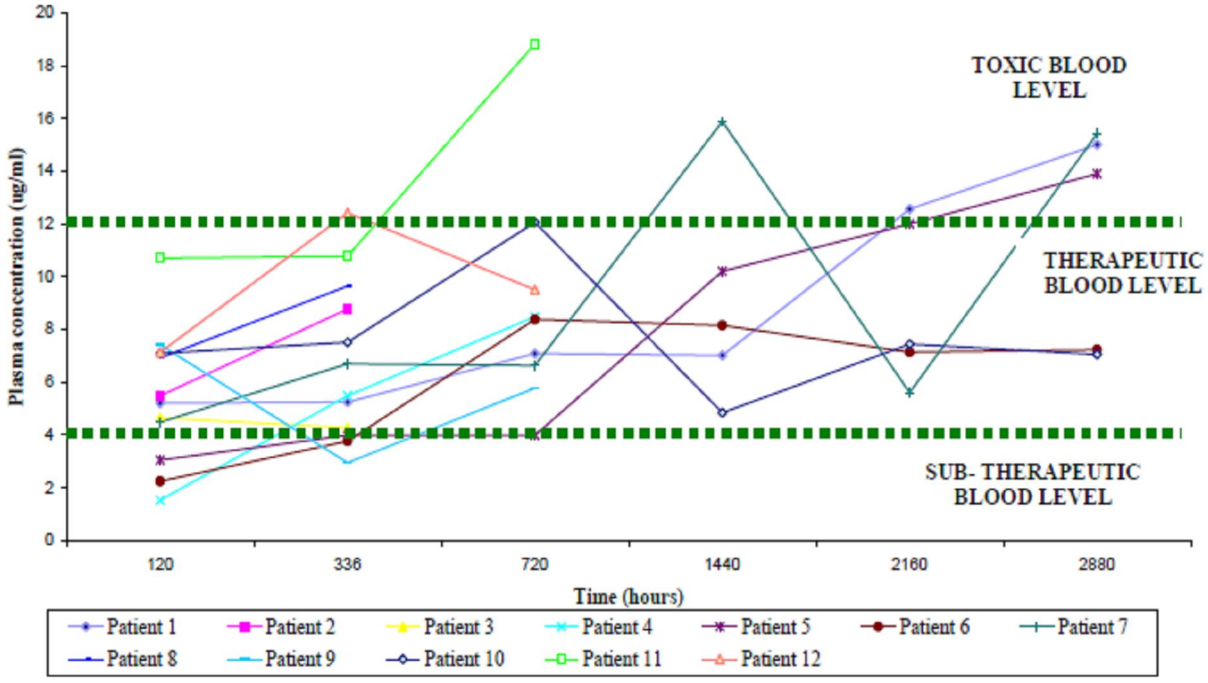

Figure 2. CBZ plasma concentration – time profile on the 5th, 15th and 30th days and on the 2nd, 3rd and 4th month of treatment.

seizure (sz) attack/s (Table 3).

The CBZ plasma concentrations after the LD of Group A were all in STR except for patient no. 7 (which is in the marginal therapeutic level) although their dose/kg body weight is comparable to Group B and C (Table 1). Patient no. 4, 5 and 7 continued having attacks after CBZ treatment, while Group B and C were fully recovered from the first week. Following the course of treatment, it is obviously manifested that 50 and 75% were free of attacks from the first week and first month respectively for Group A while Group B and C were free of attacks 100% from the first week. The main reason for this phenomenon might be that Group A had the most frequent number of attacks.

Due to the limited numbers of patients, these results do not reveal any statistical inference; however, we can say that the attacks are improved with treatment and strongly correlated with plasma concentration rather than the dose/kg body weight (Table 3).

The 2-tailed correlation analysis performed between the 7 PK parameters (Table 4a to c) and the dose per kilogram body weight (mg/kg) and per body surface area (mg/BSA) (Tables 1) for the 3 groups of PK patients, shows that there is a strong correlation between Cmax and mg/BSA; mg/kg for Groups 2 and 3, while no correlation at all for Group 1 for any of the PK parameters. Children and adults have similar PK parameters of CBZ; however, there is a poor correlation between CBZ plasma concentration and CBZ dose in children using the PK results after the LD as an indication.

Significant correlation was shown between some of the PK parameters as demonstrated in Table 5.

Adverse drug reactions

Dynamic and kinetic relationship in CBZ action

A 9 year old epileptic boy, who had seizure attack of twice/day prior to CBZ treatment, was given an initial loading dose of 120 mg followed by maintenance dose of 180 mg/day. Because of poor seizure control, his CBZ dose was increased to 300 to 420 on the 15 and 30th day, respectively.

Blood analysis of Patient no. 5 is shown in Table 6.

Although his CBZ dose was increased almost 4 folds of his loading dose (from 120 to 420), his CBZ blood level was in the sub-therapeutic range and continuously having seizure. No record showed if CBZ treatment was terminated or not.

DISCUSSION AND CONCLUSION

Epilepsy is a complex condition with high incidence in children. The cause of epilepsy in most patients is unknown (idiopathic) yet several variables like, genetic, medications of mother during pregnancy, type of delivery, habits of food intake from birth to growing period, injuries to brain during the birth, before birth or after birth etc. are documented causatives. Since many factors could be

Table 2. Number of seizures pre and post CBZ treatment.

Group	Patients number	No. of attacks pre-medication	1st – 4th day	5th – 14th day		15th – 29th day		30th day	
			MD mg/day	No. of attacks during medication per day	MD mg/day adjusted	No. of attacks per day	MD mg/day adjusted	No. of attacks per day	MD mg/day adjusted
Group A	4	1/day	180	1	120	0	180	0	180
	5	2/day	180	1	300	1	420	1	420
	6	2/day	150	0	150	0	300	0	300
	7	3/day	180	0	300	1	300	0	300
Group B	1	2/week	120	0	120	0	360	0	360
	2	1/week	240	0	360	0	540	0	540
	3	3/week	150	0	300	0	300	0	
Group C	8	2/month	150	0	180	0	180	0	270
	9	2/month	100	0	120	0	140	0	180
	10	1/month	200	0	200	0	200	0	200
	11	1/month	180	0	180	0	180	0	180
	12	2/month	72	0	144	0	144	0	240

Table 3. Correlation between numbers of attacks, CBZ dose and blood level.

Correlation		Group A 1 – 3 sz daily	Group B 1 – 3 sz/week	Group C 1 - 2 sz/month
Number of attacks pre-CBZ treatment	Dose (mg/ kg body weight)	r = -0.525	r = -0.924	r = 0.770
	Blood level (μg/ml) 5-14th day	r = 0.890	r = -0.972	r = -0.594

Table 4a. Pharmacokinetic parameters of Group 1 (ages 1 to 5 years old) patients after CBZ oral loading dose.

Patient no.	C max (μg/ml)	T max (h)	AUC [(μg/ml)/h]	Vol. Dist. (L/kg)	Ke (h^{-1})	$t_{1/2}$ (h)	Cl [(L/h)/kg]
4	1.28	2	7.56	18.39	0.027	25.20	0.50
8	2.78	8	12.7	8.15	0.056	12.37	0.46
9	3.41	6	14.53	4.20	0.088	7.87	0.37
12	3.87	4	19.75	0.90	0.174	3.98	0.16
Mean STDEV	2.835 ± 1.128	5.0 ± 2.582	13.635 ± 5.032	7.912 ± 7.591	0.086 ± 0.063	12.358 ± 9.222	0.372 ± 0.154

Table 4b. Pharmacokinetic Parameters of Group 2 (6 to 9 years old) Patients after CBZ oral loading dose.

Patient no.	C max (µg/ml)	T max (h)	AUC [(µg/ml)/h]	Vol. dist.(L/kg)	Ke(h^{-1})	$t_{1/2}$ (h)	Cl [(L/h)/kg]
1	1.23	6	7.69	1.54	0.213	3.25	0.33
5	0.91	4	5.46	15.03	0.030	23.10	0.45
10	5.27	8	19.57	2.96	0.010	6.93	0.29
11	3.18	4	20.36	1.61	0.080	8.66	0.13
Mean STDEV	2.647 ± 2.016	5.5 ± 1.915	13.27 ± 7.791	5.286 ± 6.530	0.106 ± 0.077	10.486 ± 8.706	0.301 ± 0.133

Table 4c. Pharmacokinetic parameters of Group 3 (10 to 14 years old) patients after CBZ oral loading dose.

Patient no.	C max (µg/ml)	T max (h)	AUC[(µg/ml)/h]	Vol. dist. (L/kg)	Ke (h^{-1})	$t_{1/2}$ (h)	Cl [(L/h)/kg]
2	1.89	6	11.25	5.78	0.04	16.9	0.24
3	0.43	2	2.69	13.83	0.07	9.9	0.97
6	2.23	4	15.0	2.34	0.06	11.55	0.14
7	3.83	4	25.41	2.92	0.07	10.5	0.19
Mean STDEV	2.095 ± 1.395	4.0 ± 1.633	13.587 ± 9.416	5.286 ± 6.530	0.059 ± 0.013	12.21 ± 3.20	0.385 ± 0.391

Table 5. Correlation between PK parameters of the 3 Groups of patients after loading dose.

Group	AUC vs. Cmax		AUC vs Cl		Cmax vs Cl		$t_{1/2}$ vs Ke		$t_{1/2}$ vs Vd	
	r	P	r	P	r	P	r	P	r	P
Group 1	+0.959	0.040	-0.949	0.050	-0.836	0.164	-0.853	0.147	+0.999	0.000
Group 2	+0.886	0.113	-0.828	0.171	-0.502	0.50	-0.824	0.176	+0.967	0.030
Group 3	+0.997	0.001	-0.781	0.219	-0.798	0.202	-0.993	0.001		

responsible towards causing epilepsy in children, more refined investigations and methodologies have been suggested.

Carbamazepine is more rapidly metabolized to CBZ-E in children than in adults. In children younger than 15 years of age, there is an inverse relationship between the CBZ-E/CBZ ratio and increasing age; this ratio was reported to be 0.44 in children younger than 1 year old and 0.18 in children 10 to 15 years of age (drug.com, 1998).

PK patients of Group A had 16.7 and 58% elevated hepatic liver enzymes and AlP, respectively. Patient no. 5 from group A, which was not controlled even with increase of dose up to 4 times had elevated liver enzymes, anemia and seizure attacks twice daily (Table 2).

The elevated BUN in the setting of a relatively normal Creatinine may reflect a physiological response without indicating any true injury to the kidney (normal Creatinine). However, an isolated elevation of BUN may also reflect excessive formation of urea without any compromise to the kidneys. The normal range of Na and K in all the PK and PS patients indicates that CBZ dose does not affect the patients' osmotic pressure and other metabolic activities.

Although there was a poor correlation between plasma concentration and CBZ dose in children. However in order to obtain satisfactory clinical response, CBZ plasma concentration should be measured to determine whether patients are in the therapeutic range (Drug.com, 1998).

Keeping in view all the above mentioned facts, monitoring of different variables can be helpful in optimizing the CBZ dosage in Saudi epileptic children and also in controlling the CBZ post effects and side effects of the drug.

Both AUC and Cmax are indices of exposure of patients to a given dose and may vary considerably among patients depending on factors e.g. age, gender, rate of metabolism and response to drug. In order to accurately measure AUC and Cmax, multiple blood samples are required, which are time consuming and expensive. In addition, having to deal with epileptic children, continuous blood collection, are limiting and difficult. Therefore, the approach to explore the utility of routinely collected and sparse TDM data combined with well controlled samples would allow the development of more informative population pharmacokinetic models for CBZ, which are important extensions of TDM that would

Table 6. Blood analysis of patient no. 5.

Treatment periods	CBZ dose (mg/day)	CBZ level (µg/ml)	No. of attacks		BUN	Cr	AlP	SGOT 0-42	SGPT 0- 48	WBC	RBC	Hgb
			Pre CBZ	Post CBZ	7-18	0.6-1.9	40-400			3.8-10.8	4.2 – 6.9	12-17
Initial	120	0.622		1	28.6	1.12	516	49	98	5.9	4.96	10.6
5th day	180	3.04		1	4	0.5			27			
15th day	300	3.98	2 per day	1	27	1	549	58	46	4.4	4.8	9.9
30th day	420	3.98		1	31	0.8	407	30	21	6.9	4.94	11.9

allow prediction of CBZ plasma concentration.

CBZ drug information reveals that CBZ absorption in children is slow, peak levels occur 6 to 8 h after ingestion of the first dose; the half-life ranges from 8 to 60 h; therefore, steady-state is achieved in 2 to 5 days (drug.com, 1998). In this study, $t\text{-}_{max}$ occurs 2 to 8 h, half life ranges from 3 to 23 h and steady state was achieved 5 to 30 days. Auto-induction of CBZ metabolism appeared to be complete within 1 week of starting CBZ therapy or dose change, and its degree was linearly related to CBZ daily dose.

The elimination rate constant showed a statistically significant increase with increasing drug dose. This may help explain the clinical observation that the rate of rise of steady state CBZ plasma concentrations tends to decrease with dose increase in patients taking CBZ alone (Cohen et al., 1998).

The influence of sex, weight and concomitant therapy (phenobarbitone, phenytoin and Sodium valproate) were investigated. No evidence was found that sex and politherapy significantly affected CBZ clearance (Delgado et.al. 1997).

The influence of age on clearance (Cl/F) was evaluated and was observed that older children have faster clearance compared to the younger ones (Table 4a to c).

The patients' responses to CBZ treatment show differences even to patients that were given the same dosage (Figure 1). This phenomenon maybe due to the patients' genetic variants in drug metabolizing enzymes, which have a significant effect on the way a person, responds to a drug. They can speed up or slow down enzymatic activity, or even inactivate an enzyme (Alfirevic et al., 2006).

Another possible reason maybe related to the severity of the disease or offensive loci. Group A had daily seizure attacks and Patient no. 5 did not recover until the end of study in spite of increasing the CBZ dose 4 times (Table 2).

Incidence of acute hypersensitivity syndrome (AHS) occurs 1 in 1000 to 1 in 10000 (0.1 to 0.01%) (American Board of Family Practice, 2000). In this study, it occurred in 2/12 patients (33.33%). This phenomenon could be due to inherited abnormality in the detoxification of aromatic benzene ring which is, metabolized to an arene oxide by cytocrome P450 (CYP450). Arene oxides are not metabolized and build up in the system; they bind to macromolecules and cause abnormal immune response. First-degree familial association of AHS had been documented (American Board of Family Practice, 2000). Saudi patients' increase incidence of AHS was found in first degree in two patients from the study group who experienced the same reaction.

A recent phenomenal example of pharmacogenomics clinical application is the identification of a genetic marker in patients, the human leukocyte antigen (HLA) allele HLA-B*1502, which is associated with dangerous, even fatal, skin reactions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) following treatment with the AED, CBZ. Since the HLA-B*1502 allele is found almost exclusively in patients with ancestry across broad areas of Asia. Patients who test positive for HLA-B*1502 should not be treated with CBZ unless the expected benefit outweighs the increase risk of SJS/TEN (Alfirevic et al., 2006).

Following the course of treatment, it is obviously manifested that 50 and 75% were free of attacks from the first week and 1st month respectively for Group A, while Group B and C were free of attacks 100% from the 1st week.

Due to the limited numbers of patients, these results do not reveal any statistical inference however we can say that the attacks were improving with treatment and strongly correlated with plasma concentration rather than the dose/kg body weight (Table 3).

The PK results in this study (Table 4a to c) were highly comparable to other worker's findings (Table 7) of which some were conducted on different ethnic patients, others on healthy non-Saudi adults. This similarity confirmed the importance of continuing this work using modern technology which applies non-linear random few samples which will differentiates between the actual values of CBZ PK parameters and the influence of interfering modifiers.

Table 7. Comparison of pharmacokinetic parameters findings with other workers' studies.

PK	Present study n = 12	Mahmood and Chamberlin (1998) n = 12*	Cotter et al. (1977)	Medsafe (2007)	Univ. of Virginia (1996)	Bertilsson (1998)	Cohen et al. (1998) n = 6*	Gerardin et al. (1976) n = 6*
Ke	0.03 – 0.213 0.0837 ±0.056						14.05 – 15.7	
$t_{1/2}$ (h)								
Single dose	3.25 – 25.20	18 - 55	37.5 ±13.1	36	11-30	18 - 65		37.7 ± 5.7
Multiple dose	11.68 ±6.88	5- 26		16-24 Ave: 90-10	5-14	10 - 20		21
Vd (L/kg)								
Single dose	0.90 – 18.39 6.47 ±6.022	1.4 ± 0.41	0.825 ± 0.1041	0.8 – 1.9	1- 2			
Cl [(L/h)/kg]								
Single dose	0.13 – 0.97	25 ± 5	0.0113 ± 0.0061					
Multiple dose	0.3526 ± 0.233	80 ± 30						
AUC [(µg/ml)/h]	2.69 – 25.41 13.49 ± 6.904						54.85 – 82.83	
C_{max} (µg/ml)	0.43 – 5.27 2.52 ± 1.447						7.10 – 9.92	
t_{max} (h)	2 – 8	4 – 8		2	2 - 4			
Single dose	4.83 ± 1.992	as late as 24-26						
Steady state (Css)				w/ in 2 weeks				
Relative F value	>87%	>70%						

***** Healthy volunteer

We can conclude that there is no direct relation between race and CBZ therapeutic ranges. However, by assessing the CBZ PK behavior after the LD in a representative group of the Saudi epileptic children (PK-S), this work had defined solely the genuine CBZ parameters in epileptic

Saudi children without the interference of related different variables such as food, environment, auto induction CBZ-E 10,11-epoxide and active or probably deactivating metabolites.

Study of imported pharmaceuticals used by Saudis may uncover the yet unstudied genetic and ethnic characteristics, that is, the science of pharmacogenomics. This would lead to identify specific drug therapeutic ranges for pharmaceuticals suitable to the Saudi population, which are essential for drug efficacy and safety (Islam et al. 1980).

According to National Survey of Children's Health (NSCH) report in the year 2007, epilepsy affects about 467,711 children 0 to 17 years of age in the United States. Base on FDA reports, as of September 15, 2013, there were 14,705 people reported to have side effects when taking Carbamazepine; among them, 218 people (1.48%) died (7.82% were between 0 and 19 years old). This finding emphasizes the need for performing research studies on the efficacy and safety of drugs on Saudi children.

RECOMMENDATIONS

Based on the results of the PK study, we would like to suggest the following recommendations:

1. Assumption that seizure will be controlled by giving patients a clinical dose of CBZ is a myth and far from reality.
2. Clinicians should screen at risk patients with ancestry known to exhibit the HLA-B*1502 allele before starting treatment with CBZ.
3. Plasma levels should be monitored to assure the optimal dose of CBZ in patients with epileptic disease
4. Modern technology will help to identify the CBZ PK parameters and the optimal therapeutic ranges.
5. Non-specialist doctors should be trained for a better prescription of CBZ in patients with epileptic disease.
6. Parents of these patients should be educated to ensure a better control of epilepsies in children.
7. Parents should be encouraged to follow the doctor’s instruction/s as precisely as possible.

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